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# A Review on:Solid Dispersion

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**ABSTRACT** –

Solid dispersion ,defined as the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state and an efficient technique to improve dissolution of purely water soluble drug to enhance their bioavailability .poor water solubility is one of the major problems for the various types of drugs and various approaches have been introduced for the inhancement of solubility of such drug the solubility behaviour of drug remains one of the most challenging aspects in formulation development . The number of poor water soluble compounds has dramatically increased . Currently only 10- 12% of new drug candidates have both high solubility and high permeability. More 60-65% of potent drug products suffer from poor water solubility solid dispersion have attracted considerable interest as an efficient means for improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs . Compared to conventional formulation such as tablets or capsules, solid dispersion which can be prepared by various methods have many advantages. Few of the aspects are to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterisation. In this review , an over view on solid dispersions in general will be given with emphasis on the various types of the solid dispersions, manufacturing process, characterisation, advantages, disadvantages and the application of the solid dispersions, challenges in formulation of solid dispersion dosage forms, and various types of marketed preperations.

Keywords: (Introduction, Solubilization enhancement Technique,Solid Dispersion,Method of Prepration)

**INTRODUCTION :**

The oral route of drug administration is the most well-known and favored route of conveyance due to accommodation and simplicity of ingestion. From a patient's possibility, gulping a measurement structure agreeable method for taking medicine.Therefore, patient consistence is more viable with orally managed meds as contrasted and different routes of administration, for instance, parenteral route. Albeit the oral route of administration is liked, in the event of many drugs it tends to be a risky and wasteful method of conveyance for various reasons.

Restricted drug ingestion bringing about helpless bioavailability is among the potential issues that can be survived while conveying a functioning specialist through the oral route.

In the wake of controlling a drug orally, it initially disintegrates in gastric media and afterward pervades the layers of the GI tract to arrive at foundational dissemination.

In this manner, a drug with poor watery solvency will regularly display disintegration rate restricted assimilation, and a drug with helpless layer penetrability will ordinarily display penetration rate restricted retention.Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include:

- Enhancing solubility and dissolution rate of poorly water-soluble drugs and
- Enhancing permeability of poorly permeable drugs. Solubility is a predetermined and rate limiting step for absorption.

Restricted a Drug needs to enter in to the foundational course to apply its helpful impact. In later advancements, development of combinatorial science and high throughput screening (HTS) can viably find the new drugs which show great pharmacological exercises. Notwithstanding, 35-40 % of these new drugs found by those advancements experience the ill effects of poor fluid solvency.

In the Biopharmaceutical Classification System (BCS) **(table 1 and figure 1)** drugs with high membrane permeability and low aqueous solubility are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly for improving the oral absorption and bioavailability of BCS Class II drugs.

Solid dispersion technique was firstly demonstrated by Sekiguchi and Obi .[1]

| Class | Dissolution in aqueous environment | Permeation over (intestinal) membrane |
|---|---|---|
| I | Fast | Fast |
| II | Slow | Fast |
| III | Fast | Slow |
| IV | Slow | Slow |

**Table :1 Biopharmaceutical Classification System**

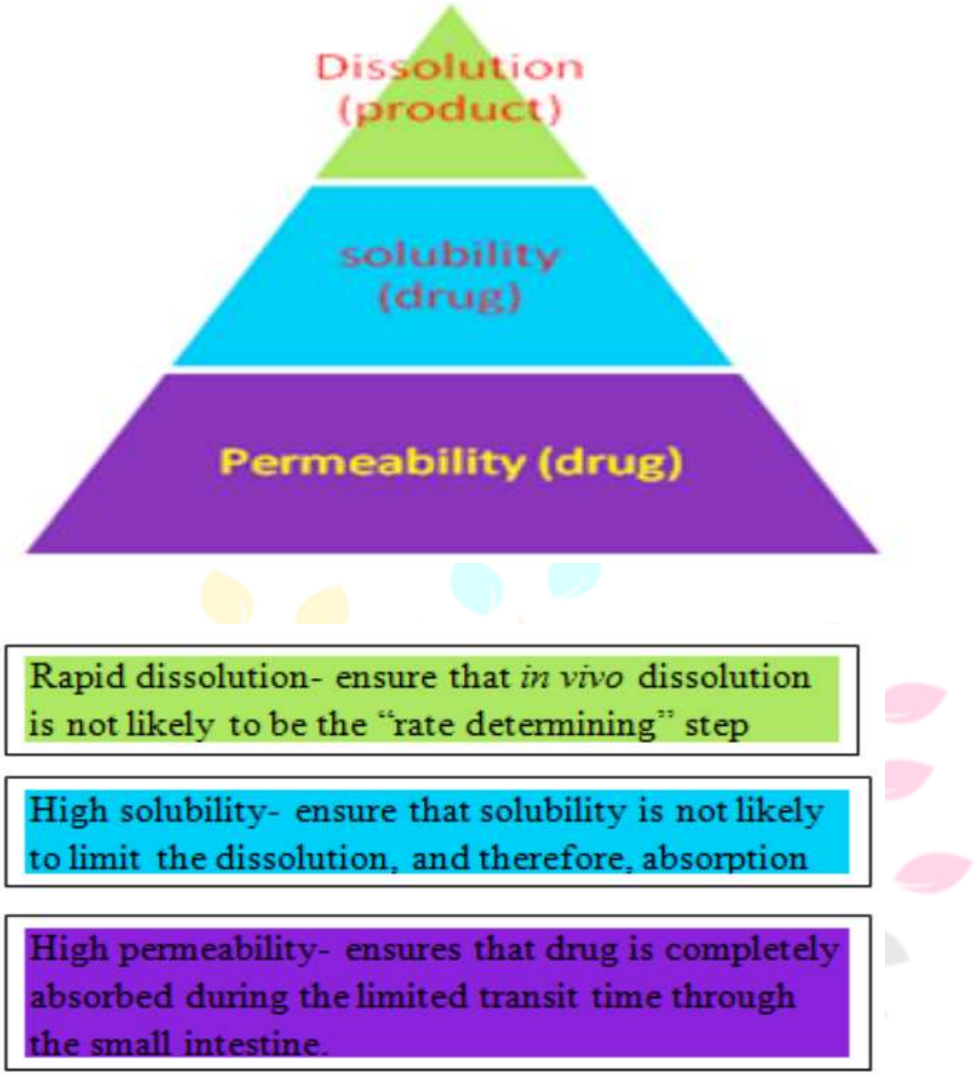



**Figure :1 Bcs Class Boundaries**

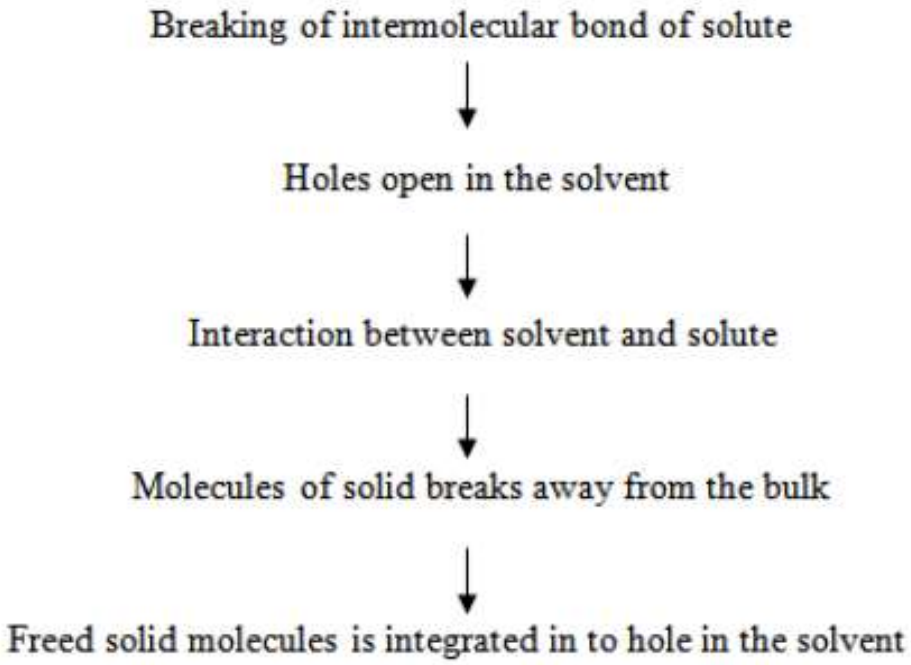
**Class-I -** Drugs disintegrate quickly in a watery climate and are quickly shipped over the retaining layer. No methodologies are needed to expand their ingestion.When the arrival of the dynamic fixing from the detailing is more slow than the gastric discharging rate, great in-vitro-in-vivocorrelation (IVIVC) can be anticipated.

The absorption (pace) of **class-II** drugs can be expanded by speeding up the disintegration. Class-II drugs show In-vitro – In-vivo Correlation (IVIVC) as long as the in-vivo disintegration rate is same as invitro. Notwithstanding, in light of the fact that the disintegration rate is basic for class-II drugs, the in-vivo ingestion can be impacted by a few physiological vacillations, similar to the volume and pH of the digestive squeezes, the presence of bile salts, food, proteins, and microbes, the motility of the stomach and the thickness in the stomach lumen. For **class-III** drugs the absorption is rate limiting and in-vitro dissolution experiments cannot be used to predict in-vivo absorption. Additionally for **class-IV** drugs no IVIVC can be anticipated. It is up to the plan researcher to expand the degree of ingestion yet additionally to work on the IVIVC. This will lessen the patient-to-patient changeability and work on the bioavailability and the consistency of pharmacokinetic boundaries.[2]

The expression **"strong scattering"** alludes to the scattering of at least one dynamic fixings in a latent transporter in a strong state, oftentimes ready by the dissolving (combination) technique, dissolvable

strategy or combination dissolvable strategy. The drug can be scattered microscopically, in shapeless particles (groups) or in translucent particles.[4, 5]

## Process Of Solubilisation :[6]




## Solubility enhancement techniques:

1. **Nanonization:**

   Nanoemulsions present huge o/w interfacial regions and fundamentally low interfacial strains. According to the writing, Nanoemulsions have made plasma fixation and bioavailability profiles of drugs more reliable. Nanonization are utilized for transformation of drug molecule in to nano-precious stones having the size of 200-600nm.

2. **Supercritical fluid recrystallization (SCF):**

   Those liquids have temperature and pressure greater than its critical temperature and pressure so as properties of gas and fluid. By this strategy drugs are solubilize. It can be re-crystallized with reduction of particle size of pharmaceutical chemicals.[7]

3. **Use of surfactant:**

   Permeability and disintegration rate can be increased be surfactant.Surfactant are three sorts; anionic, cationic and non-ionic. Anionic and cationic select over the non-ionic surfactant. It goes about as great solubilizing specialist.

4. **Evaporative precipitation:**

This technique includes stage partition for nucleation and development of miniature or nano particle happens. Warmed arrangement showered through atomizing spout and surfactants are added for reduction of particle size. Fine particles are produced which work on the solubility and permeability of drug..[8]

5. **Micronization:**

Reduction of particle size happen so as increase of surface area which increase the disintegration rate and bioavailability of drug .The particle size after micronization is 1-10 microns. This technique includes splash drying and attrition strategy.

6. **Sonocrystallisation:**

This method used for the reduction of particle size by use of ultrasound and liquid solvent. It is a new method for increasing of solubility .[9]

7. **Nanomorph technology:**[10,11]

In this method crystalline state of less water soluble drugs change in to amorphous state. Drug particles are reduced under high tension and high velocity by applying of shear power. By this peculiarity drugs particles get scattered. Homogenization relies upon pressure and nature of drug.[12]

8. **Solid dispersion:**

Chiou and Riegelman scatterings as "the scattering of one or more dynamic Ingredients in an idle excipient or lattice, where the dynamic ingredients could exist in finely glasslike, solubilize, or shapeless detail"

Strong scattering is the main strategy for improving of solubility of ineffectively water dissolvable drugs. It additionally increases the bioavailability by actual alteration.[13]

## Factor Affecting Drug Absorption:[14]

**Pharmaceutical factors:** It includes physiological properties of drug substances and formulation factors. Physicochemical properties of drug substances.

- Drug solubility & dissolution rate
- Particles size & effective surface area
- Polymorphism
- Solvates & hydrates
- Salt form of drug
- Ionization state
- Drug pka & lipophilicity

**Formulation Factors:**

- Disintegration time
- Manufacturing variables
- Method of granulation
- Compression force
- Nature & type of dosage form
- Pharmaceutical ingredients
- Product age & storage conditions

**Patient related factors i.e., physiological factors:**

Membrane physiology:

- Nature of cell membrane
- Transport processes

Gastro-Intestinal motility:

- Gastric emptying rate
- Intestinal motility
- Drug stability in GIT
- pH of GIT
- Surface area of GIT
- Intestinal transit
- Blood flow to GIT.
- Effect of food

**Solubility:**

The solubility of substance is the sum that has passed into arrangement when balance is achieved between the arrangement and abundance, i.e., undissolved substance, at a given temperature and pressure. The substance to be broken up is called as 'solute' and the dissolving liquid where the solute is disintegrated is called as 'dissolvable', which together structure a 'answer'. Definition of different solubility terms is given in table.

**Table :2 Definition of different solubility term.[15]**

| Description forms (solubility definition) | Parts of solvent required for one part of solute | Solubility range (mg/ml) | Solubility assigned (mg/ml) |
|---|---|---|---|
| Very soluble (VS) | <1 | >1000 | 1000 |
| Freely soluble (FS) | 1 to 10 | 100 -1000 | 100 |
| Soluble | 10-30 | 33-100 | 33 |
| Sparingly soluble (SPS) | 30-100 | 10-33 | 10 |
| Slightly soluble (SS) | 100-1000 | 1-10 | 1 |
| Very slightly soluble (VSS) | 1000-10000 | 0.1-1 | 0.1 |
| Practically insoluble (PI) | >10000 | <0.1 | 0.01 |

## Types of Solid Dispersions:

1. On the basis of carrier used [18]
2. On the basis of their molecular arrangement [19]

Based on transporter utilized: based on transporter utilized strong scatterings can be grouped into three ages:

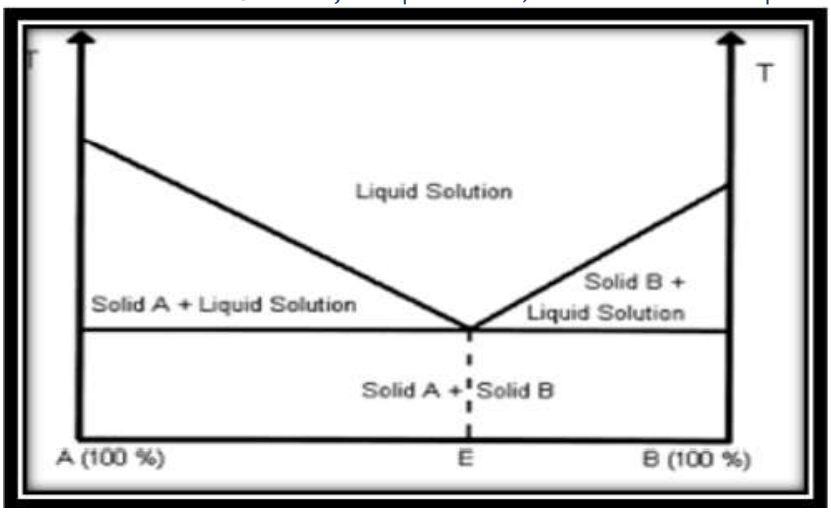
**First generation:** Utilizing glass like transporters, for example, urea and sugars, original strong scatterings were arranged which were the first transporters to be utilized in quite a while. They have the negative marks of shaping glass like strong scatterings and didn't deliver the medication as fast as formless ones.

**Second generation:** Second generation strong scatterings incorporate shapeless transporters rather than translucent transporters which are generally polymers. These polymers incorporate manufactured polymers, for example, povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates just as normal items based polymers, for example, hydroxylpropylmethyl-cellulose (HPMC), ethyl cellulose, and hydroxypropylcellulose or starch subsidiaries like cyclodextrins.

**Third generation:** As of late, it has been shown that the disintegration profile can be improved assuming the transporter has surface action or self-emulsifying properties.

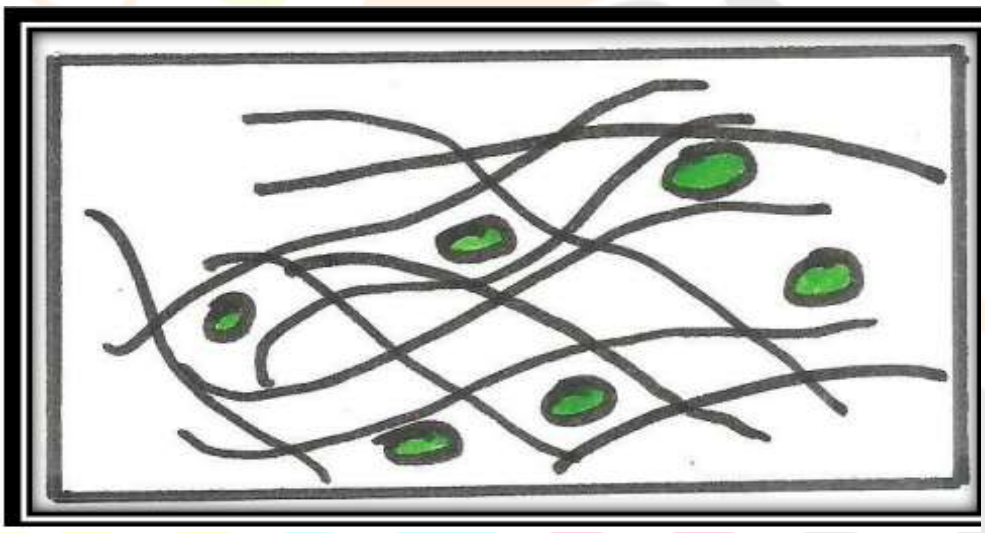
On the basis of their molecular arrangement: Solid dispersions can be classified in following types:

**Eutectics Systems:** This mixture comprises of two mixtures which in the fluid state are totally miscible however in the strong state just to an extremely restricted degree. By quick hardening of the combined soften of two parts these are ready and that show total fluid miscibility and minor strong dissolvability as displayed in Fig 2.20




**Phase diagram of an Eutectic System**

**Amorphous precipitation in a crystalline carrier:** In the crystalline transporter the drug may likewise encourage in a nebulous structure rather than synchronous crystallization of the drug and the transporter (eutectic framework). The indistinct strong state is displayed in fig 3. The high energy condition of the drug in this framework by and large delivers a lot more noteworthy disintegration rates than the relating crystalline types of the drug.[16]



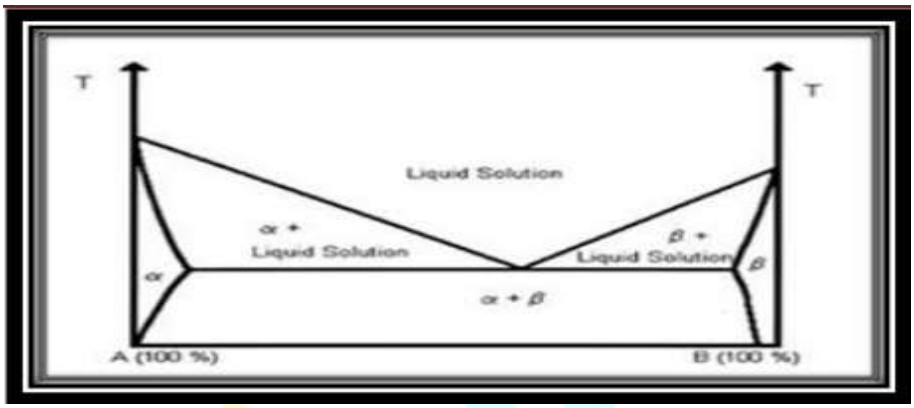
**Amorphous solid solution**

**Glass solutions and suspensions:** These are the homogeneous lustrous system wherein solute is broken up in glass transporter. Glass suspensions are mixtures in which encouraged particles are suspended in glass dissolvable. Grid energy is a lot of lower in glass arrangements and suspensions.[20]

**Solid Solutions:** In this system a homogeneous one phase system is formed when the two components crystallize together. The particle size of the drug is reduced to its molecular size in the solid solution. Thus, a faster dissolution rate is achieved in a solid solution than the corresponding eutectic mixture.[21]

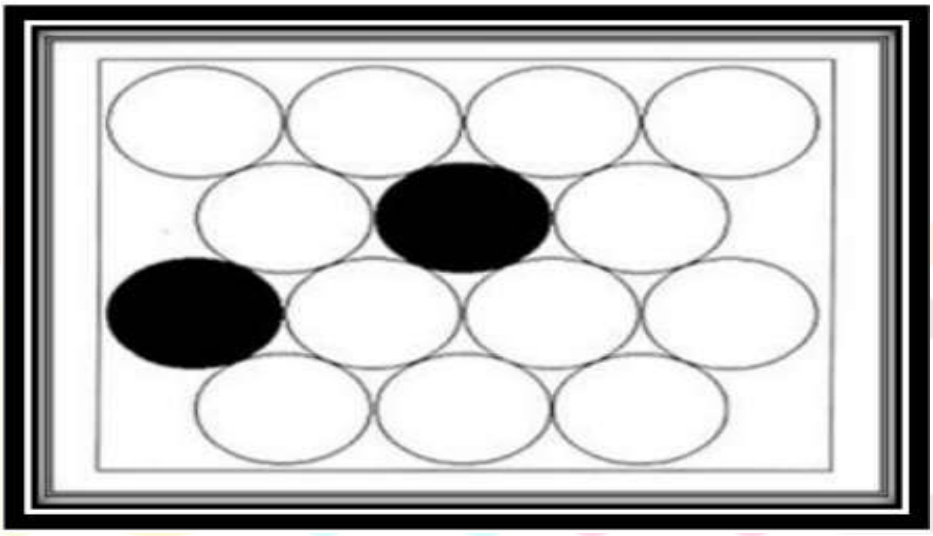
**Continuous Solid Solutions:** The components are miscible in all proportions in a continuous solid solution. Hypothetically, this means that stronger the bonding strength between the two components than the bonding strength between the molecules of each of the individual components.[22]

**Discontinuous Solid Dispersions:** [14] The solubility of each of the components in the other component is limited in the case of discontinuous solid solutions. A typical phase diagram (Fig.4) shows the regions of true solid solutions. One of the solid components is completely dissolved in the other solid component in these regions.




**Phase Diagram for Discontinuous solution**

**Substitutional crystalline solid solutions:** A substitutional crystalline solid dispersion is depicted in Fig. 5 in which the solute molecules substitute for the solvent molecules in the crystal lattice. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules. [14,20]



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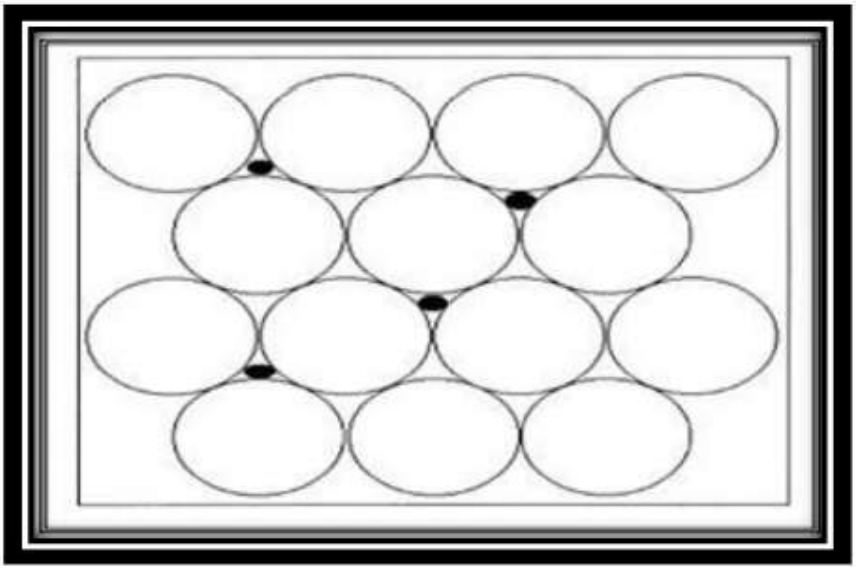
**Substitutional crystalline solid solution**

**Interstitial Crystalline Solid Solution:**[14,20] In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent in the crystal lattice as shown in Fig 6. The solute particles should have a molecular diameter that is no greater than 0.59 occasions than that of the dissolvable molecular diameter and the volume of the solute atoms should be under 20% of the dissolvable. Interstitinal Crystalline strong arrangement.



**Interstitinal Crystalline solid solution**

## Advantages of solid dispersion:

**Particles with Reduced Particle Size** Molecular dispersions, as strong dispersions, represent the keep going state on molecule size decrease, and after transporter disintegration the drug is molecularly scattered in the disintegration medium.[23]

**Particles with Improved Wettability:** Carriers with surface movement, for example, cholic corrosive and bile salts.Carriers can impact the drug disintegration profile by direct disintegration or co-solvent effects.

**Particles with Higher Porosity:** Particles in solid dispersions have been found to have a more serious level of porosity. The expanded porosity of solid scattering particles likewise rushes the drug discharge profile.

**Drugs in Amorphous State:** Poorly water soluble crystalline drugs, when in the undefined state will generally have higher solvency.[24] For drugs with high precious stone energy, higher nebulous compositions can be acquired by picking carriers, which show explicit collaborations with them.

## Disadvantages of solid dispersion:

Despite extensive expertise with solid dispersions, they are not comprehensively utilized in commercial items, primarily on the grounds that there is the likelihood that during handling (mechanical pressure) or capacity (temperature and stickiness stress) the nebulous state might go through crystallization.[25,26] .This might bring about diminished dissolvability and disintegration rate.[27] Therefore, double-dealing of the maximum capacity of shapeless solids requires their adjustment in solid state, just as during in-vivo execution.[28]

The limitations of this technology have been a drawback for the commercialization of solid dispersions The limitations include:

- Laborious and expensive methods of preparation,
- Reproducibility of physicochemical characteristics,
- Difficulty in incorporating into formulation of dosage forms,

- Scale-up of manufacturing process, and
- Stability of the drug and vehicle.

- **Applications of solid dispersions**[30,31]

1. To build the dissolvability of poorly soluble drugs subsequently increment the disintegration rate, ingestion and bioavailability.

2. To balance out unsteady drugs against hydrolysis, oxidation, recrimination, isomerization, photograph oxidation and other decomposition methodology.

3. To reduce a side effect of certain drugs.

4. Masking of unpleasant taste and smell of drugs.

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

6. To avoid undesirable incompatibilities.

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

## Evaluation of physicochemical properties of solid dispersion: [32,33,34]

**• Phase Solubility**

Concentrate on It is done within the sight of polymer (transporter) utilizing shaking carafe technique. Then, at that point, test is sifted and examined by UV spectrophotometer for assurance concentration of drug.

**• Saturation Solubility Study:**

Drug and solid scattering clumps are included abundance amount in 25 ml refined water up to its super immersion

**• Drug content:**

Known amount of solid scattering is broken up in a solvent and afterward dissected by UV spectrophotometer for assurance of drug content.% drug stacking and % ensnarement productivity is determined by following condition, % Drug stacking = (Weight of drug in solid scattering powder)/(Weight of solid scattering powder) X 100 - - - - - (1)

## Polymeric Carrier Used in Solid Dispersion:

**Polyethylene glycol (PEG):**[35]

Polyethylene glycol is the polymer of oxidized ethylene and is generally straightforward or white solid. It is generally utilized as a mixture with different substances because of its remarkable properties. By and large, it is relied upon to get the ideal structure, viscosity, liquefying point, and water-dissolvability by blending the substance in with PEG. Specifically, for poorly water-soluble drugs, PEG can give further developed hydrophilicity, subsequently bringing about higher bioavailability. Stake commonly utilized in solid dispersions by and large are of molecular load of 1500~20000 (Leuner and Dressman, 2000.[36]

**Polyvinylpyrrolidone (PVP):**

Polyvinylpyrrolidone is the polymerized result of vinylpyrrolidone and by and large has molecular weight going from around 2,500 to 3,000,000. In addition, PVP with its inward amide bond has comparative construction with protein overall, which implies it has high bioaffinity. Along these lines, oral bioavailability would be improved by taking solid dispersions arranged with PVP (Leuner and Dressman, 2000; Ning and Sun et al., 2011).

**Polyvinylalcohol (PVA), crospovidone (PVP-CL), polyvinylpyrrolidone-polyvinylacetate copolymer (PVP-PVA):**

The three polymers, PVA, PVP-CL, and PVP-PVA, all have a place with the polyvinyl bunch. The disintegration rate is demonstrated to be multiple times quicker in solid dispersions when PVA is added as a transporter (Suzuki and Sunada, 1998

**Polyacrylates and polymethacrylates:**

Polyacrylates and polymethacrylates are polymers of acrylic corrosive and methacrylic corrosive. They are likewise utilized as polymeric transporter in making solid scattering. For similar reason, subsidiaries with different straightforward useful gatherings to these polymers are as often as possible utilized

**Urea :**

Urea, not the same as the previous polymers, is a substance which as of now exists in our body. As a previous substance which is a definitive structure not long before protein item is discharged after digestion, it has less danger for its harmful impact than different substances. Notwithstanding, in spite of the fact that there is clear improvement in drug's disintegration rate assuming urea is utilized as transporter (Okonogi and Oguchi et al., 1997), its adequacy in further developing the drug discharge rate is no greater than with different polymers like PVP or PEG.[37]

**Sugar, polyols and their polymers:**

Sugar and polyols have great water solvency as there are numerous hydroxyl bunches in their design. As they as of now exist in our body and are utilized through digestion, sugars can be considered as having no serious poisonousness. For example, a few arrangement techniques incorporate the most common way of making mixture of framework and drug with very high temperature .However, there are a couple of drugs which were demonstrated to show further developed drug discharge property when utilizing sugar or polyols as transporter (Ali and Gorashi, 1984; Jachowicz, 1987; Okonogi and Oguchi et al., 1997).

**Emulsifiers:**

Emulsifying specialists further develop drug bioavailability through two components. Most importantly, they can further develop drug's wettability which can expand drug disintegration rate, consequently further developing bioavailability

**Organic acids and their derivatives:**

Natural acids, for example, nicotinamide, citrus extract, succinic corrosive and their subordinates with changing useful gatherings can be utilized as carriers of solid dispersions. They assist with further

developing drug's bioavailability by speeding up the drug's delivery rate. There are a few investigates which distinguished that drug r (Goldberg and Gibaldi et al., 1966; Chiou and Riegelman, 1969; Suzuki and Sunada, 1997; Suzuki and Sunada, 1998).[38,39]

## Preparation of Solid Dispersions:

Various methods are used for preparation of solid dispersion system. These methods are depicted in figure: 8.[40]

1. Fusion / Melting method
2. Solvent method
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomeration Process
7. The use of surfactant
8. Electrospinning
9. Super Critical Fluid (Scf)

### 1. Fusion method:

The liquefying or combination strategy is the readiness of actual mixture of a drug and a water-soluble transporter and warming it straightforwardly until it softens. A portion of the resources to overcome these issues could be warming the actual mixture in a fixed container or dissolving it under vacuum or in presence of idle gas like nitrogen to forestall oxidative corruption of drug or transporter.[40,41]

### 2. Solvent method:

The initial phase in the solvent technique is the planning of an answer containing both network material and drug. The second step includes the expulsion of solvent(s) bringing about arrangement of a solid scattering. Low drug concentrations are utilized to break down both drug and framework material in water, however this requires vanishing of huge measures of solvent, making the cycle costly and illogical[42,40,43]

### 3. Melting solvent method (melt evaporation):

It includes planning of solid dispersions by dissolving the drug in an appropriate fluid solvent and afterward incorporating the arrangement straightforwardly into the liquefy of polyethylene glycol, which is then dissipated until an unmistakable, solvent free film is left. From a reasonable viewpoint, it is simply restricted to drugs with a low helpful portion for example under 50 mg and especially valuable for drugs that are thermolabile or have high softening focuses.[40,44]

### 4. Melt extrusion method:

Hot-stage expulsion (HME) consists of the expulsion, at high rotational speed, of the drug and transporter, recently blended, at softening temperature for a little timeframe. Solid scattering by this strategy is composed of dynamic fixing and transporter, and get ready by hot-stage expulsion utilizing a co-pivoting

twin-screw extruder. The drug/transporter blend is at the same time dissolved, homogenized and afterward expelled and molded as tablets, granules, pellets, sheets, sticks or powder.[43,41]

5. **Lyophilization Technique (Freeze-drying):**

Lyophilization has been thought about a molecular blending strategy where the drug and transporter are co broken up in a common solvent, frozen and sublimed to acquire a lyophilized molecular scattering. This strategy was proposed as an elective method to solvent dissipation.[43,41]

6. **Melt Agglomeration Process:**

This procedure has been utilized to plan solid scattering wherein the folio goes about as a transporter. Also, solid dispersions are arranged either by warming cover, drug and excipient to a temperature over the liquefying point of the fastener (dissolve in technique) or by showering a scattering of drug in liquid folio on the warmed excipient (splash on methodology) by utilizing a high shear blender.[40]

**The use of surfactant:**

The utility of the surfactant systems in solubilization is vital. Adsorption of surfactant on solid surface can alter their hydrophobicity, surface charge, and other key properties that administer interfacial cycles like flocculation/scattering, drifting, wetting, solubilization, detergency, and improved oil recovery and corrosion hindrance.[40]

**Electrospinning:**

Electrospinning is an interaction where solid strands are created from a polymeric liquid stream arrangement or dissolve conveyed through a millimeter-scale nozzle. This cycle includes the utilization of a solid electrostatic field over a conductive narrow appending to a supply containing a polymer arrangement or dissolve and a conductive collection screen.[40,41]

**Super Critical Fluid (Scf) Technology:**

The supercritical liquid antisolvent procedures, carbon dioxide are utilized as an antisolvent for the solute yet as a solvent concerning the natural solvent. Various abbreviations were utilized by different creators to denote micronization processes: spray solvent extraction system, precipitation with a compressed liquid antisolvent, gas antisolvent, arrangement upgraded scattering by supercritical liquids and supercritical antisolvent.[40,43]

## Characterization of solid dispersion:

A few distinctive molecular constructions of the drug in the grid can be encountered in solid dispersions. A few strategies have been accessible to explore the molecular course of action in solid dispersions.[45]

**Powder X-ray diffraction:**

Powder X-beam diffraction can be utilized to subjectively distinguish material with long reach request. More keen diffraction tops show more crystalline material.

**Infrared spectroscopy (IR):**

Infrared spectroscopy (IR) can be utilized to distinguish the variety in the energy appropriation of associations among drug and lattice. Sharp vibrational groups show crystallinity.[46]

**Water fume sorption:**

Water fume sorption can be utilized to separate among indistinct and crystalline material when the hygroscopicity is different.[47] This strategy requires precise information on the hygroscopicity of both completely crystalline and completely nebulous examples.

**Isothermal Microcalorimetry:**

Isothermal microcalorimetry measures the crystallization energy of shapeless material that is warmed over its glass progress temperature (Tg).[48]

**Disintegration calorimetry:**

Disintegration calorimetry estimates the energy of disintegration, which is reliant upon the crystallinity of the sample.[49] Usually, disintegration of crystalline material is endothermic, though disintegration of nebulous material is exothermic.

**Macroscopic strategies:**

Macroscopic strategies that action mechanical properties that are diverse nebulous and crystalline material can be demonstrative for the level of crystallinity. Thickness estimations and Dynamic Mechanical Analysis (DMA) decide the modulus of versatility for and viscosity and along these lines impacted by the level of crystallinity. In any case, additionally these procedures require knowledge about the additivity of these properties in personally blended twofold solids.

**Differential Scanning Calorimetry (DSC):**

Oftentimes utilized procedure to distinguish how much crystalline material is Differential Scanning Calorimetry (DSC).[50] Moreover, the liquefying and (re)crystallization energy can be measured. The softening energy can be utilized to distinguish how much crystalline material.

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