

## A Review on Solid Dispersion: A Technology for improving bioavailability.

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Submitted: 15-07-2022

Accepted: 30-07-2022

### ABSTRACT

To improve dissolution of poorly water-soluble drugs and thus enhancing their bioavailability, the dispersion of one or more active pharmaceutical ingredients in a carrier at solid state is used. This process is known as solid dispersion. It has engrossed significant interest as an efficient meal of improving the dissolution rate. It happens due to dispersion of poorly water-soluble drugs with water-soluble carriers. The one of the most challenging aspects in formulation development is solubility behaviour of drugs. The number of poor water soluble as radically increase. Compare to conventional formulations such as tablets on capsule, solid dispersion prepared by various methods can be used which have many benefits over the above conventional dosage form. For the preparation of solid dispersion, few of the aspects are to be considered such as; selection of carrier and methods of physicochemical characterization. In this review, an emphasis is put on solubility, various types of solid dispersion, BCS classification, carriers, solid dispersion techniques, mechanism to enhanced dissolution in solid dispersion, characterization, advantages, disadvantages and the applications of the solid dispersion.

**Keywords:** Carriers, Solid dispersion, Solubility, Solid dispersion techniques, Solubility enhancement.

### I. INTRODUCTION

Modern drug discovery techniques, with advances in combinatorial chemistry and high throughput screening, continue to fill drug development pipelines with a high number of poorly soluble New Chemical Entities (NCEs). It is estimated that over the years about 40%–70% of NCEs are poorly water soluble and large number of scientists are engaged in invention of NCEs and the success rate is poor. A drug with poor aqueous

solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. 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 drug and enhancing permeability of poorly permeable drugs.

The main possibilities for improving dissolution are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions. Of these possibilities, changes in the hydrodynamics are difficult to invoke in vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the luminal fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipient, results to date have not been particularly encouraging.

Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media.

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.<sup>3</sup>The basic principle involved in enhancing the poor solubility of drug with solid

dispersion includes complete removal of drug crystalline structure and its molecular dispersion in a hydrophilic polymeric carrier.

Though many routes of drug administration are there but the oral drug delivery is the most preferred route due to ease of administration, patient compliance, flexibility in formulation, etc. However, in case of the oral route there are several bottlenecks such as limited absorption of poorly water-soluble drugs from gastrointestinal tract resulting in low bioavailability and poor pharmacological response. Most of the new chemical entities under development now-a-days are intended to be used as a solid dosage form that originates an effective and reproducible in-vivo plasma concentration after oral administration due to many advantages of this route like greater stability, smaller bulk, accurate dosage and easy production

But what the fact remains is that huge number of new chemical entities are highly lipophilic /poorly water-soluble drugs, and are not well absorbed after oral administration, so the oral delivery of such drugs is frequently associated with low bioavailability, high intra/inter-subject variability, and a lack of dose proportionality. To overcome the problem of low solubility associated with such drugs, various strategies till date have been applied to enhance solubility including pro-drug formation,  $\beta$ -CD complexation, use of surfactants, micro-nidation, salt formation, etc. One such formulation approach that has significantly enhanced solubility/ dissolution of such drugs is solid dispersion (SD) technology.

The term 'Solid Dispersion' refers to a group of solid products consisting of at least two different components, generally 'a Hydrophobic Drug and a Hydrophilic Carrier'. The carrier can be either crystalline or amorphous. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug gets released as fine colloidal particles and as a result there is enhancement of solubility/dissolution rate of poorly water-soluble drugs.

The drugs which are having poor water solubility they often show poor oral bioavailability due to the low levels of absorption. Drugs that undergo dissolution rate limited absorption, their dissolution rate can be enhanced by micritisation or size reduction but this leads to aggregation of particles which leads to poor wettability. Various other approaches for increasing the bioavailability of poorly water-soluble drugs include salt formation, solubilisation using a co- solvent, complexation with cyclodextrin and particle size

reduction; all these approaches have various limitations. Development of solid dispersions of poorly bioavailable drugs overcame the drawbacks of the previous approaches. Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophilic) at solid state prepared by melting (fusion) method, solvent, or melting solvent method. When the solid dispersion comes in contact with the aqueous medium, the inert carrier dissolves and the drug is released, the increased surface area produces a higher dissolution rate thus increasing the bioavailability of the poorly soluble drug.

#### ADVANTAGES OF SOLID DISPERSION

1. Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches. Chemical approaches to improving g bioavailability without changing the active target can be achieve by salt formation or by incorporating polar ionizable groups.
2. Solid dispersions appear to be better approach to improve drug solubility than these techniques because they are easier to produce and more applicable.
3. In molecular dispersion solid dispersion represent the last state on practical size reduction and after carrier dissolution the drug is molecularly dispersed in the dissolution medium.
4. Solid dispersion also provides practical with improved wettability as it was observed that even carriers without any surface activity such as cholic acid and bile salts when used can significantly increase the wettability property of drug.
5. Particles in solid dispersion have been found to have a higher degree of porosity.
6. The increase in porosity also depends on the carrier properties for instance solid dispersion containing linear polymers produce larger and more porous particles than those containing reticular polymers.
7. One of the most important advantages of solid dispersion is drugs interacting with hydrophilic carriers can decrease agglomeration and release in supersaturation state resulting in rapid absorption and improve BA.
8. Solid dispersion can improve drug wettability and increase the surface area resulting in enhanced aqueous solubility of the drugs.

9. Solid dispersion can be produced as a solid oral dosage form which is more convenient for patients than the other forms like liquids products.
10. In addition showed an advantage compared to salt formulation co crystallization and other methods. for examples salt formulations use ionized active pharmaceutical ingredients (APIs) (cationic or anionic form) and are widely used in the pharmaceutical industry due to the broad capacity of design according to desired drug properties.
11. However not all drugs can be ionized with all cations/anions and phase dissociation or stability issue is inherent in salt formation
12. Poorly water-soluble crystalline drugs when in the amorphous state tend to have higher solubility the enhancement of the drug release can usually be achieved using the drug in its amorphous state.

#### **DISADVANTAGES OF SOLID DISPERSION:**

1. Despite extensive expertise with solid dispersion they are not broadly used in commercial products mainly because of possibility of the change of amorphous state to the crystalline state.
2. The effect of the moisture on the storage stability of the amorphous pharmaceuticals is also a significant concern because it may increase drug mobility and also promote drug crystallization.
3. Most of the polymers used in solid dispersion can absorb moisture which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state.
4. Another drawback of solid dispersion is their poor scale up for the purposes of manufacturing. Strategies to overcome the manufacturing process drawbacks will be discussed later.
5. Solid dispersion shows changes in crystallinity and decreased dissolution rate with aging.
6. Due to their thermodynamic instability, solid dispersion is sensitive to temperature and humidity during storage.
7. These factors can promote phase separation and crystallization of solid dispersion by increasing the overall mobility decreasing the glass transition temperature or disrupting interaction between the drug and carrier resulting in decreased solubility and dissolution rate of the drug.
8. Patients suffering from cancer should continue to use anticancer drugs during the treatment.

However, the instability of solid dispersion during the period of storage can affect drug quality and the effectiveness of the treatment.

9. Exploitation of the full potential of amorphous solid requires their stabilization in the solid state.
10. Solid dispersions is their poor scaleup for the purposes of the manufacturing.

#### **Classification Of Solid Dispersion:**

##### **1) Simple Eutectic mixture:**

Simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only a very limited extent in the solid state It is prepared by rapid solidification of fused melt of two component that show complete liquid miscibility but negligible solid- solid solution

##### **2) Amorphous precipitation in crystalline matrix:**

This is similar to simple eutectic mixture but only difference is that drug is precipitate out in an amorphous form

##### **• Solid solution**

In case of solid solution, the drugs particle size has been reduced to its absolute minimum Depending on the miscibility the two types of solid solution are:

#### **CONTINUOUS SOLID SOLUTIONS:**

In continuous solid solutions, the components are miscible in all proportions i.e., the bonding strength between the components is stronger than the bonding between the individual component. Discontinuous solid solutions:

In discontinuous solid solutions, the solubility of each of the component in the other component is limited in nature.

#### **DEPENDING ON THE DISTRIBUTION OF THE SOLVATES IN THE SOLVENT SOLID SOLUTION CLASSIFIED AS FOLLOWS:(2)**

##### **Substitutional solid solution:**

Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules. These are those solid solution which have a crystalline structure, the solute molecules substitute for the solvent molecules in the crystal lattice.

##### **Interstitial crystalline solid solution:**

In interstitial solid solution, the dissolved molecules occupy the interstitial spaces between

the solvent molecules in the crystal lattice. Solute molecules diameter should be less than 0.59 times than that of the solvent molecular diameter

**Glass suspension:**

Glass suspension are mixture in which precipitated particles are suspended in glass solvent lattice energy is much lower in glass solution diameter. The term glass refers to a pure chemical or a mixture of a pure chemicals in the glassy state.

**Glass solution:**

Glass solution are homogeneous glassy system in which solute dissolves in glass carrier

**SELECTION OF THE CARRIER:(2)**

A carrier should possess the following characteristics to be suitable for increasing the rate of dissolution of a drug

- The carrier should be freely soluble in water with a high rate of dissolution
- It should be nontoxic in nature
- It should be pharmacologically inert
- Should possess heat stability with a low melting point
- It should be able to enhance aqueous solubility of the drug
- Economical Materials used as carrier are given in table

S. No.	Category	Carriers
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose
2	Acids	Citric acid, succinic acid
3	Polymeric materials	Polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragit L100, eudragit E100, eudragit RL, eudragit RS
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans
6	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins

different carriers used in solid dispersion

**SELECTION OF SOLVENTS:**

Solvent to be included for the formulation of solid dispersion should have the following criteria:

- Both drug and carrier must be dissolved.
- Toxic solvents to be avoided due to the risk of residual levels after preparation e.g., chloroform and dichloromethane
- Ethanol can be used as alternative as it is less toxic.
- Water based systems are preferred.
- Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to

consideration. Common solvents used are given in table

Solvent	Melting Point(°C)	Boiling Point(°C)	Vapour pressure at 25°C (pka)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
Chloroform	-63	62	26.1
DMSO	19	189	0.08
Acetic acid	17	118	1.64

**Table: - Different solvents used insolid dispersion**

**SOLUBILITY:(3)**

The solubility of substance is the amount that has passed in to solution when equilibrium is attained between the solution and excess that is undissolved substance at the given temperature and pressure. The substance to be dissolved is called 'solute' and the dissolving fluid in which the solute is dissolved is dissolve is called as 'solvent', which together form a 'solution'. Definition of different solubility terms is given in table.

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

**Table: - different solubility terms**

**BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS):(3)**

The BCS was first devised in 1995 by Amidon and his co-workers. According to the BCS, drug substances can be classified as given in Table 4.

<b>Class I</b>	<b>High Solubility, High Permeability</b>
<b>Class II</b>	<b>Low Solubility, High Permeability</b>
<b>Class III</b>	<b>High Solubility, Low Permeability</b>
<b>Class IV</b>	<b>Low Solubility, Low Permeability</b>

**Table: - Classification of drugs as per BCS system**

By increasing the solubility and dissolution rate of the class II drug in the gastrointestinal fluids the bioavailability may be

enhanced. Particularly for drugs with low gastrointestinal solubility drug release is a crucial and limiting step for oral drug bioavailability. It is possible to enhance their bioavailability and reduce side effects, by improving the drug release profile of these drug. Model list of Essential Medicines of the World Health Organization (WHO) has assigned BCS classification on the basis of data available in the public domain. Orally administered drugs out of 130 on the WHO list, 61 could be classified with certainty. 84% of these drugs belong to class I, 17% to class II, 39% to class III and 10% to class IV. The class II & class IV compounds are highly dependent on the bioavailability which ultimately depends on solubility. Thus, a greater understanding of dissolution and absorption behaviour of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products

#### Classification Of Solid Dispersion On The Basis Of Recent Advancement:

##### 1) First Generation solid dispersion:

These solid dispersions are prepared by using crystalline carriers. Urea and sugars were the first crystalline carriers that were used in the preparation of solid dispersions. These have a disadvantage of being thermodynamically unstable and they do not release drug at a faster rate.

##### 2) Second Generation solid dispersion:

These solid dispersions are prepared using amorphous carriers instead of crystalline carriers. The drug is molecularly dispersed in the polymeric carrier. The polymeric carriers are divided into two groups:

a. **Synthetic polymers-** povidone, polyethylene glycols and polymethacrylates

b. **Natural polymers** – hydroxy propyl methyl cellulose, ethyl cellulose, starch derivatives like cyclodextrin.

##### 3)Third Generation solid dispersion:

These solid dispersions contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These achieve the highest degree of bioavailability for the drugs that are having poor solubility. The surfactants being used in the third-generation solid dispersion are such as inulin, poloxamer 407 etc.

#### Polymers Used In The Solid Dispersion:

##### 1)Polyethylene glycol (PEG):

- These are compounds are obtained from a reaction of ethylene glycol with ethylene

oxide. PEGs whose molecular weight is above 300000 are commonly termed as polyethylene oxides.

- For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500-20,000 are usually employed. As the MW rises, so does the viscosity of the PEG.
- At MW of up to 600, PEGs are fluid, in the range 800 -1500 they have a consistency that is best described as Vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20,000 and above form hard, brittle crystals at room temperature.
- Their solubility in water is generally good, but reduces with MW. A meticulous advantage of PEGs for the solid dispersions is that they have good solubility in numerous organic solvents.

The melting point of the PEGs of interest with an average molecular weight of 4600 (range 4400-4800) is 57 - 61°C and with an average molecular weight of 6000 (range 5000-7000) 60 – 63°C.

##### 2)Polyvinyl pyrrolidone (PVP):

- PVP molecular weight ranges from 2500 to 300000.
- It is having solubility in solvents like water, ethanol, chloroform and isopropyl alcohol.
- PVP gets decomposed at high temperature therefore it is not suitable for preparation of solid dispersions prepared by melt method because melting takes place at a very high temperature.
- PVP can be classified according to the K value, which is calculated using Friendster's equation.
- The temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (T<sub>g</sub>) is high; for example, PVP K25 has a T<sub>g</sub> of 1558°C.
- For this reason, PVPs have only restricted application for the preparation of solid dispersions by the hot melt method. Due to their excellent solubility in an ample variety of organic solvents, they are mostly suitable for the preparation of solid dispersions by the solvent method.

##### 3)Cellulose derivatives:

###### a)Hydroxypropyl methylcellulose (HMPC):

- HPMCs are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are

methylated and 4-32% is derivatized with hydroxypropyl groups.

- The molecular weight of the HPMCs ranges from about 10000 to 1 500 000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane.

#### **b)Hydroxypropyl cellulose (HPC):**

- Hydroxypropyl cellulose (HPC) exhibits good solubility in a range of solvents, including water (up till 400C), ethanol, methanol and chloroform.
- The average MW of the HPCs ranges from 37 000 (Type SSL) to 1 150 000 (Type H).

#### **c)Hydroxypropyl cellulose (CMEC):**

- CMEC also belongs to the cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions.
- It dissolves readily at pH values above 5-6, with lowest dissolution pH being dependent on the grade of the CMEC.
- CMECs also dissolve readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixture of dichloromethane and ethanol.

#### **d)Hydroxypropyl methylcellulose phthalate (HPMCP):**

- HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55).
- They are having a type-dependent solubility in organic solvents. The dissolution rate of griseofulvin at pH 6.8 could be greatly enhanced by incorporating it in a evaporate of HPMCP

#### **4)Polyacrylates and polymethacrylates:**

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles.

- In pharmaceuticals they are mainly used as coatings to change the release of the drug from the dosage form.

#### **5)Phospholipids:**

- The complexity of glycerides advances by modification of the terminal hydroxyl with

phosphate linked head groups to form phospholipids, common phospholipid head groups include choline, ethanolamine, serine, inositol and inositol phosphate, and glycerol esters.

- As with the triglycerides, numerous species are possible by various combinations of different head groups and fatty acyl substitution at the first and second positions of the glycerol backbone, fluidity differences are evident as a function of the gel to liquid crystalline transition temperatures.
- Solubility of phospholipids is intimately linked to the confirmation of the aggregate material rather than strictly a chemical function of the molecule.
- Monoaryl phospholipids, which tend to form micelles, are usually more readily soluble in aqueous solutions.

#### **6)Sugar, polyols and their polymers:**

- Although sugars and related compounds are highly water soluble and have few, if any, toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions.
- The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare evaporates.
- Even with these drawbacks, several attempts have been reported to prepare solid dispersions using sugars and their derivatives.
- Mannitol, which has a melting point of 165-168°C and decomposes only above 2500°C, can be employed in some cases to prepare dispersions by the hot melt method.

#### **7)Organic acids and their derivatives:**

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin method.

#### **Cyclodextrins:**

Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment

#### **Advantages of Cyclodextrins:**

1. Increasing the stability of the drug
2. Release profile during gastrointestinal
3. Transit through modification of drug

4. Release site and time profile
5. Decreasing local tissue irritation.
6. Masking unpleasant taste

### MECHANISM OF ENHANCED DISSOLUTION IN SOLID DISPERSION:

A number of factors may influence or increase the dissolution rate for solid dispersion. These factors include the following: -

#### a) Reduced Particle size or Reduced Agglomeration:

Both are related to reduction of particle size and increase in the exposed surface area of the drug. Size reduction has been considered to be result of eutectic or solid solution formation. It has also been suggested that to the dissolution medium as physically separate entities the presentation of particles may reduce aggregation. For solid dispersion many of the carriers used may have some wetting properties and may lead to reduce agglomeration and increase surface area by improved wetting.

#### b) Increased solubility or Dissolution rate of the drug:

The solubility of the drug may increase by using many of the carriers. Therefore, carrier controlled the release of drug that is controlled by the carrier and is independent of drug properties. Secondly some system shows release behaviour that is dependent on the properties of the drug rather than polymer.

#### c) From crystalline to amorphous state transformation/ Formation of high Energy State:

Amorphous drugs have the higher energy state, minimum stability and can be considered as cooled liquids. The energy required to transfer a molecule from crystal is greater than required for non-crystalline (amorphous) solid so they have greater aqueous solubility than crystalline forms. For example, the solubility of amorphous state of novobiocin is 10 times more than crystalline form.

#### d) Wetting:

The liquid forms a film over the surface of the solid when a strong affinity exists between a liquid and solid. When this affinity is non-existent or weak the liquid has difficulty displacing the air and there exist an angle of contact between the liquid and the

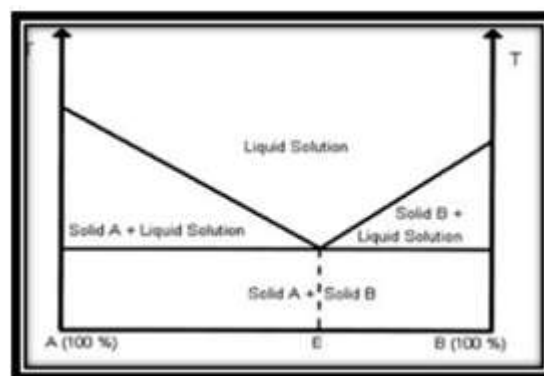
solid. This contact angle results from an equilibrium involving three interfacial tensions.

### Characteristics Of Solid Dispersion:

#### 1) Drug carrier miscibility:

##### a) Differential scanning calorimetry:

- This technique is often used to detect the amount of crystalline material.
- In this technique, samples are heated with a constant heating rate and the amount of energy necessary for that is detected.
- With DSC the temperature at which thermal events occur can be detected.
- Thermal events can be a glass to rubber transition, recrystallization, melting or degradation. The melting energy can be used to detect the amount of crystalline material.



#### b) Water vapour sorption:

- If hygroscopicity is different water vapour sorption can be used to differentiate between crystalline and amorphous material.
- It requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

### 2) Solubility Enhancement:

#### a) Solubility studies:

Solubility studies are done for the finding out the solubility behaviour shown by the solid dispersion system in different types of solvent system and body fluids.

### 3) Microscopic Techniques:

#### a) Dynamic mechanical Analysis:

Dynamic mechanical analysis (DMA) that measures mechanical properties can be indicative for the degree of crystallinity.

**b) Recent Advances:**

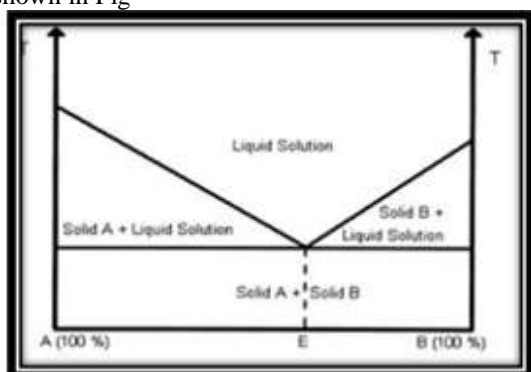
As we know that solid dispersion technology has tremendous potential for increasing the bioavailability of drug. Successful development has been possible in recent years due to availability of few surfaces active and self-emulsifying carriers with relatively low melting points and because of easy manufacturing process filling of drugs along with carrier into hard gelatine capsules.

**TYPES OF SOLID DISPERSION:(6)**

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

**1)Eutectics Systems:**

This mixture consists of two compounds which in the liquid state are completely miscible but in the solid state only to a very limited extent. By rapid solidification of the fused melt of two components these are prepared and that show complete liquid miscibility and minor solid-solid solubility as shown in Fig



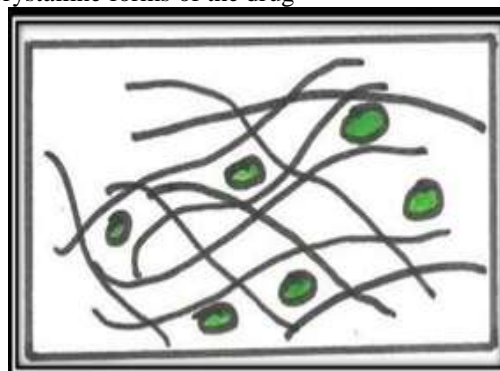
**Fig: - Phase diagram of a Eutectic System**

Thermodynamically, such a system is an intimately blended physical mixture of two crystalline components. When the mixture of A and B with a fix composition is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. When a mixture containing slightly soluble drug and carrier as an inert substance and highly water soluble is dissolved in an aqueous medium, the carrier will dissolve fast, releasing very fine crystals of the drug

**2)Amorphous precipitation in a crystalline carrier:**

In the crystalline carrier the drug may also precipitate in an amorphous form instead of

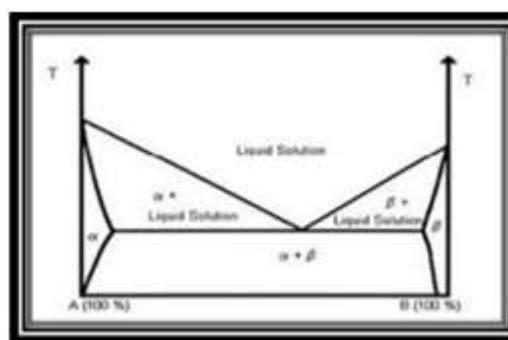
simultaneous crystallization of the drug and the carrier (eutectic system). The amorphous solid state is shown in Fig. 2. The high energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug



**Fig: - Amorphous solid solution**

**3)Discontinuous Solid Dispersions:**

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.3) shows the regions of true solid solutions. One of the solid components is completely dissolved in the other solid component in these regions. The mutual solubilities of the two components start to decrease below a certain temperature. Goldberg reported that the term 'solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.



**Fig: Phase Diagram for Discontinuous solution**

**4)Substitutional crystalline solid solutions:**

A substitutional crystalline solid dispersion is depicted in Fig. 4 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.



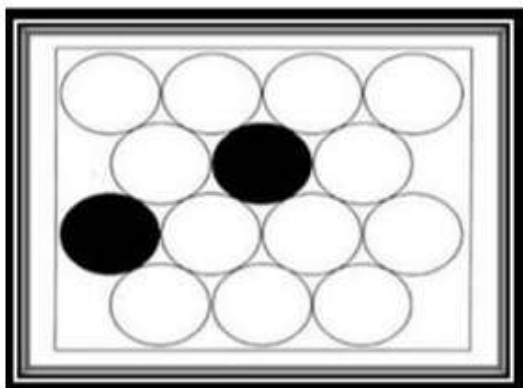


Fig: - Substitutional crystalline solid dispersion

### 5) Interstitial Crystalline Solid Solution:

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent in the crystal lattice as shown in figure. The solute molecules should have a molecular diameter that is no greater than 0.59 times than that of the solvent molecular diameter and the volume of the solute molecules should be less than 20% of the solvent.

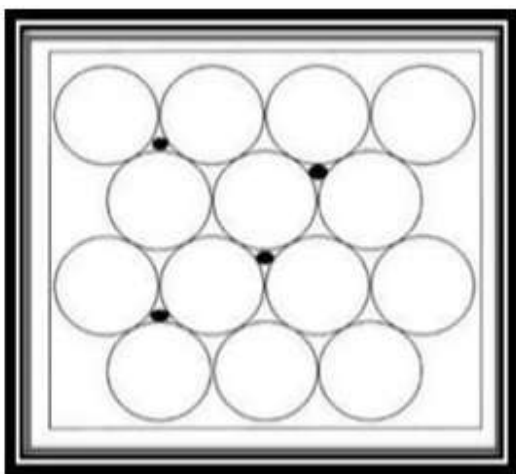


Fig: - Interstitial Crystalline solid solution

### METHODS OF SOLID DISPERSION:(7)

#### 1. Kneading Technique: -

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.

#### 2. Solvent evaporation method: -

In this method, both drug and carrier are dissolved in organic solvent. After entire dissolution, the solvent is evaporated. The solid mass is ground, sieved and dried. Ex. Solid

dispersion of furosemide with eudrilids was prepared by solvent evaporation method.

#### 3. Co-precipitation method: -

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

#### 4. Melting method: -

Drug and carrier are mixed using mortar and pestle. To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components. It is then cooled to acquire a congealed mass. It is crushed and sieved. Ex. albendazole and urea solid dispersion was prepared by this method.

#### 5. Co-grinding method: -

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Ex. Chlordiazepoxide and mannitol solid dispersion was prepared by this method.

#### 6. Gel entrapment technique: -

Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then drug for example is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved.

#### 7. Spray-Drying Method: -

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer.

#### 8. Lyophilization Technique: -

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative method to solvent evaporation. Lyophilization 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.

#### 9. **Electrospinning Method: -**

The electrospinning technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology. In this procedure, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces prevail over the surface tension of the drug/polymer solution at the air interface, fibres of submicron diameters are produced. As the solvent evaporates, the formed fibres can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandrel. This technique has tremendous potential for the preparation of nanofibers and controlling the release of biomedicine, as it is simplest and the cheapest this technique can be utilized for the preparation of solid dispersions in future.

#### 10. **Dropping method solution: -**

The dropping method, is to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the methods. For laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation (Bashiri et al., 2003).

#### 11. **Melt Extrusion Method: -**

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a corotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g., sustained-release pellets.

#### 12. **Melt Agglomeration Process: -**

This technique has been used to prepare Solid Dispersion where the binder acts as a carrier.

SD(s) is prepared either by heating the binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration because of easier control of the temperature and because higher binder content can be incorporated in the agglomerates.

#### **Applications Of Solid Dispersions:(9)**

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.

It is possible that such a technique be used:

- 1) To obtain a homogeneous distribution of a small amount of drug in solid state
- 2) To stabilize the unstable drug.
- 3) To dispense liquid or gaseous compounds in a solid dosage.
- 4) To formulate a fast release primary dose in a sustained released dosage form.
- 5) To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- 6) To reduce pre systemic inactivation of drugs like morphine and progesterone. Polymorphs in a given system can be converted into isomorphism, solid solution, eutectic or molecular compounds.
- 7) To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
- 8) To stabilize unstable drugs against hydrolysis, oxidation, racemization, isomerisation, photo oxidation and other decomposition procedures.
- 9) To reduce side effect of certain drugs.
- 10) Masking of unpleasant taste and smell of drugs.
- 11) Improvement of drug release from ointment, creams and gels.
- 12) To avoid undesirable incompatibilities.
- 13) To obtain a homogeneous distribution of a small amount of drug in solid state.
- 14) To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- 15) To formulate a fast release primary dose in a sustained released dosage form.
- 16) To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- 17) To reduce pre systemic inactivation of drugs like morphine and progesterone.

## II. LIMITATIONS:

- They are not broadly used in commercial products because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization / re-crystallization.
- The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization.

## III. CONCLUSION:

As from the project, it is clear that the solid dispersion technology is one of the advance approaches to resolve the problem of solubility of poorly water-soluble drugs. As with the increasing number of poorly soluble drugs candidates the need for improvements in the drug manufacturing technology seems to be a promising solution for improving the dissolution characteristics of such drug. Also, the method of preparation and the ratio of carrier to drug also play vital role in the solubility / dissolution rate enhancement of drug. We have attempted in bringing all the things aspects to achieve this goal. Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs. So, in the novel drug delivery applications, solid dispersion technology will continue to developed in future solve problems associated with the delivery of poorly soluble drugs.

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