



## **A Review on Solubility Enhancement by Solid Dispersion Technique**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Approximately 30% of drug are lipophilic from all the newly discovered drug molecules and thus because of poor aqueous solubility fails to reach the market. In systemic circulation for achieving the desired therapeutic response solubility is one of the rate-limiting factors for orally administered drugs. The major challenge for the formulation scientist is to overcome the problem of solubility which can be achieved by using various technical approaches for the formulation product development. For enhancing the solubility of drugs Solid dispersion, micronization, and salt formation are some of the necessary approaches employed for enhancing the solubility of poorly soluble drugs and each approach has its merits and limitations. To deliver poorly soluble drugs novel technologies like Nanosuspension, Supercritical processing, and Cryogenic technologies may have various major opportunities. For the formulation development of new drug solubility behavior of any drug can be the most challenging aspect. The current review is focused on the solid dispersion technique for enhancement of solubility of drug which will be a novel technique for enhancing the solubility to diminish the amount of poorly soluble drug candidates eliminated from development and its characterization.

**Keywords:** *Solid dispersion; bioavailability; solid dispersion generation; carrier selection; amorphous; crystalline.*

## 1. INTRODUCTION

In 1961 Sekiguchi and Obi first discussed on the use of solid dispersion for reducing particle size and thus enhancing the dissolution and absorption rate [1]. Among all the dosage forms used for drug administration, solid dosage forms have the advantages of their greater stability, smaller bulk, accurate amount of dosing, and ease of production [2]. Despite many advantages of oral dosage form, there are many reasons that some of the drugs can be problematic and it has an insufficient mode of delivery. The attributes are poor drug absorption, rapid degradation of drug and lamination in peptides and proteins that results in insufficient concentration, distribution of the drug to different tissues having higher toxicity of drug, Poor drug solubility, and plasma level fluctuation leads to bioavailability that cannot be easily predictable [3-5].

### 1.1 Characteristics of Amorphous Solid Dispersion (ASD)

1. It is widely applicable to acidic, basic, neutral, and zwitterionic nature of drugs.
2. For evaluating the efficacy and safety minimum amount of API (Active Pharmaceutical Ingredient) is required.
3. Resources required to reduce the preclinical supply can be reduced.
4. Useful in investigating the alternate pathways in bioavailability enhancement.
5. Quick onset of action because of rapid drug dissolution.
6. Improve exposure (enhance bioavailability, quick onset, and reduce dose).

Various factors which cause poor solubility are, high crystallinity/high melting point, Zwitterion formation, Insoluble salts, H-bonding network, Hydrophobicity/High log P, Lack of ionisable group, Higher molecular weight [6,7].

## 2. SOLID DISPERSIONS GENERATIONS

Solid dispersion is characterized in three generations on the bases of solid dispersion technologies:

### 2.1 First Generation Solid Dispersions

For the preparation of first-generation solid dispersion, crystalline carriers were used. Sugar and urea were the first carriers used in solid dispersion. These are having the disadvantage that they form crystalline solid dispersion that is

thermodynamically stable but drug release does not occur as that of amorphous form [8,9].

### 2.2 Second Generation Solid Dispersions

In second-generation solid dispersion, the carriers used are amorphous for the preparation of solid dispersion. The amorphous carriers are categorized as fully synthetic polymers and polymers based on natural products. Fully synthetic polymers generally include polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), and polymethacrylates. Polymers based on natural products are cellulose derivatives such as hydroxypropyl methylcellulose (HPMC), ethylcellulose, or hydroxyethylcellulose and starch derivative such as cyclodextrin. Because of forced solubilization of carrier drug is in the supersaturated state in second-generation solid dispersion. Thus in this system, the drug particle size can be reduced to molecular level for solubilizing or by co-dissolving the drug in the water-soluble carrier, thus providing better wettability and drug dispersibility by carrier material and thus producing the amorphous form of drugs or carrier [6, 10].

### 2.3 Third Generation Solid Dispersions

During the current research, it has been proved that the dissolution profile of drug can be improved if the carrier is having the surface activity of self-emulsifying properties. This leads to the formulation of third-generation solid dispersion. They generally consist of surfactants or a mixture of amorphous polymers or surfactants as a carrier. Thus the third generation solid dispersion has become to improve the highest level of bioavailability of poorly water-soluble drugs and thus the solid dispersion is stabilized by avoiding the recrystallization of drug. Different types of surfactants such as inulin, inutec SPI, compritol 888 ATO, gelucire 44/14, and PVP K30, poloxmer 188 have been shown as an effective carrier for the origination of high polymorphic purity and *in vivo* bioavailability enhancement. [8,11,12].

## 3. TYPES OF SOLID DISPERSION

### 3.1 Eutectic Mixtures

Eutectic mixtures of solids are usually prepared by high-speed cooling of commonly of compounds for obtaining physical mixtures of very translucent crystals of two compounds [13,14].

### 3.2 Solid Solution

In solid solution, inhomogeneous one-phase system, there is together crystallization of two components. In solid solution, the particle size of drug is diminished to molecular size. Thus a solid solution can attain a rapid dissolution rate apart from corresponding eutectic mixtures [15,7].

### 3.3 Discontinuous Solid Solutions

The solubility of each component is limited to another component as a discontinuous solid solution. The region of a true solution is shown in a typical phase diagram. There is the complete dissolution of one component in other solid components in these regions. The interchangeable solubilities of two components start to dissolve below a certain temperature [16,17].

There are two types of solid dispersion based on the way according to the solvate molecules are distributed in the solvendum. These are as:

#### 3.3.1 Substitutional crystalline solutions

Solute molecules act as a substitute (in the crystal lattice of solid solvent) in the solvent molecule in this type of solution. Both continuous and discontinuous solution can be prepared by this method. As per the possible size of solute and solvent have similar dimensions [13,18].

#### 3.3.2 Interstitial crystalline solid solutions

The dissolved molecule occurs in the interstitial space between the crystal lattice in the interstitial

solid solution. It forms a discontinuous solid state [19]. There should be less than 20% volume of solute molecule [20].

### 3.3.3 Amorphous Solid Solutions

The dispersion of solute molecules molecularly in amorphous solid dispersion, but irregular arrangement within the amorphous solvent. This method is identical to the eutectic mixture but the difference is the precipitation of the drug in amorphous form [20,21,22]. Chiou and Rieglman were the scientists who first reported the formation of amorphous solid dispersion, thus improving the dissolution properties of the drug.

### 3.4 Glass Solutions and Glass Suspensions

It refers to a homogenous glassy system in which a solute dissolves in the glassy solvent. The term glass describes one of two, a pure chemical or mixture of chemicals in a glassy translucent state. The glassy or translucent state can be obtained by quenching of the melt. This can be characterized as lucidity and brittleness under the glass transition temperature. There are multi-ingredient glassy systems in a glass solid solution that consists of one phase. It is homogenous and uniform at the molecular level. In this system, the carrier usually occurs in an amorphous state, while the dissolved molecules are molecularly dispersed [9, 10, 23].

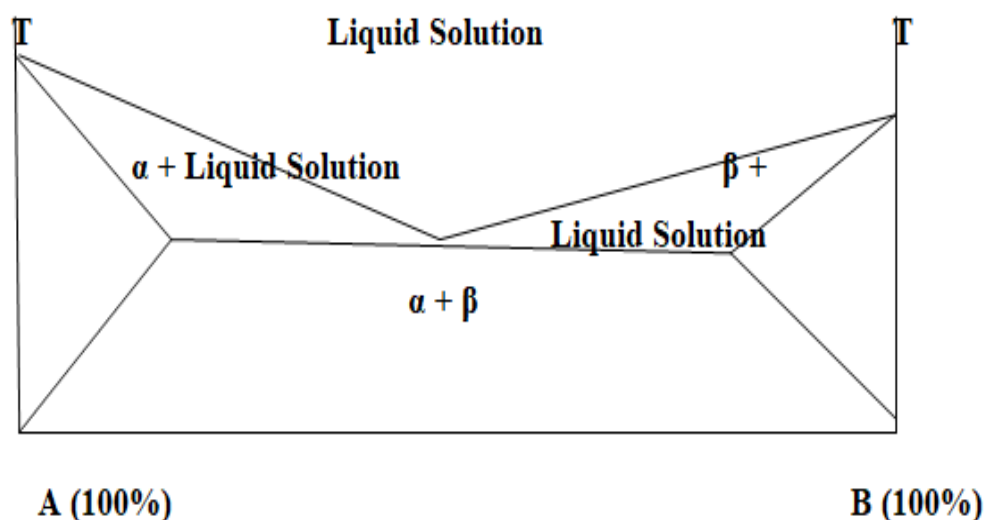


Fig. 1. Hypothetical diagram representing discontinuous solid solution

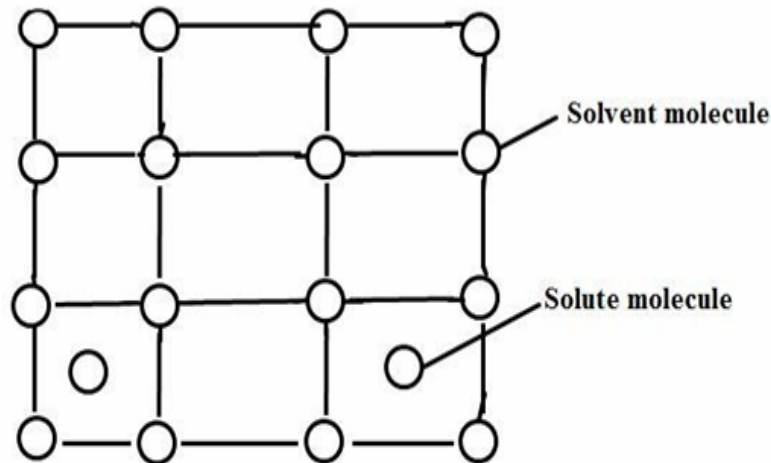


Fig. 2. Phase diagram of interstitial crystalline solid solutions

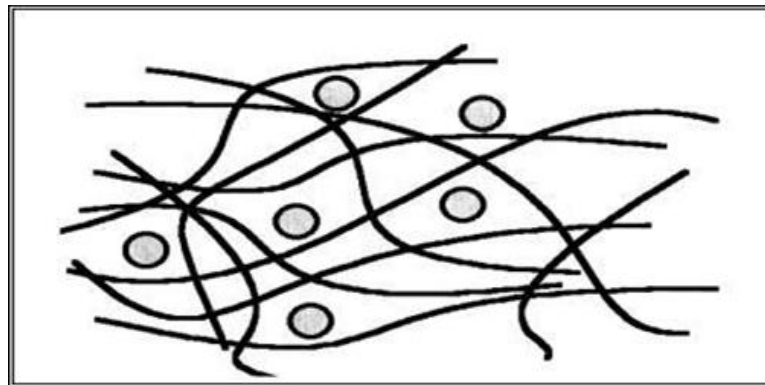


Fig. 3. Phase diagram representing amorphous solutions

### 3.5 Choice of a Carrier

For increasing the dissolution rate of drug following criteria should be met by the carrier of drug:

1. It has intrinsic rapid dissolution property and is freely soluble in water.
2. It is non-toxic and is pharmacologically inert in nature.
3. It is heat stable and has a low melting point for the melt method.
4. It is soluble in the different types of solvents and can pass from a glassy state upon evaporation for the solvent method.
5. It can enhance the water solubility of drug.
6. It has chemical compatibility with the drug but does not lead to the formation of a strongly bonded complex with drug [24,25,26].

The different types of carriers employed in solid dispersion and their behavior has been described in table as:

Table 1. Carriers used in solid dispersion

Sr. No	Carriers	Nature
I	Sucrose, Lactose, Sorbitol, Dextrose, Galactose	Sugar
II	Succinic Acid, Citric Acids	Acids
III	Polyethylene Glycol, Hydroxypropyl Methyl Cellulose, Hydroxy Ethyl Cellulose, Povidone, Galactomannan, Pectin	Material is Polymeric in nature
IV	Phthalate, Eudragit RS, Hydroxy Propyl Methyl Cellulose	Insoluble or Enteric Polymer

### 3.6 Selection of Solvents

The solvents which are introduced in the formulation of solid dispersion must have below mentioned characteristics:

1. Both drug and carrier should be soluble.
2. Because of the risk of residual level toxic solvents must be avoided after preparation. Eg: Chloroform and Dichloromethane.
3. Ethanol is less toxic, so it can be used as an alternative.
4. There should be a preference for a water-based system.
5. Specific care must be taken into consideration while using the surfactant as carrier drug solution because they lead to a reduction of the glass transition temperature, [27,28]

## 4. METHODS OF SOLID DISPERSION PREPARATION

The two major processes used for preparing solid dispersion are the melting method and solvent evaporation method.

### 4.1 Melting Method

Sekiguchi et. al. firstly applied the melting method in which the drug is melted within the carrier and thus follows the refrigerating and grinding of the product obtained [29,30]. On whole, heating of all the constituents above the melting and glass transition temperature then follows the mixing and cooling is melting method [31]. This constantly mixed mass is then allowed for cooling at room temperature or under cold conditions. The cooling rate thus has a greater influence on the attributes and stability of solid

dispersion. For the process of cooling and solidification, ice bath agitation [32], solidification inside desiccator on pretidish in room temperature [33], spreading of plates placed over dry ice [34,35,36], immersion of liquid nitrogen [37] or stored in desiccators had been used. Major requirement in the method is that there should be the stability of drugs and carriers at room temperature. To obtain the processing temperature the carrier used should have a low melting point ( $T_m$ ) or ( $T_g$ ) and lead to a decrease in the potential of drug degradation.

### 4.2 Hot Stage Extrusion

Hot-Stage Extrusion (HSE) consists of extrusion and having a high carrier and drug rotational speed and for a short period, it is previously mixed at melting temperature [38]. In this process, there is entrapment of drug in a polymer during shaping the central composite to the formulation product. In the dispersion, there is always 40% (w/w) drug concentration. This technique is identical to the fusion method. The major difference in this method is that during intense mixing the component is introduced by the extruder. In extruder high local temperature is because of high shear forces and for heat-sensitive material this may be problematic.

### 4.3 Melt Agglomeration

In this technique of solid dispersion preparation binder usually acts as a carrier. In this technique firstly binder gets heated, drug and excipients to a temperature higher than the melting point of the binder. For melt agglomeration, the rotary process has become the most preferable as the temperature is easier to control from it and thus there is the incorporation of high binder content in the agglomerates [39].

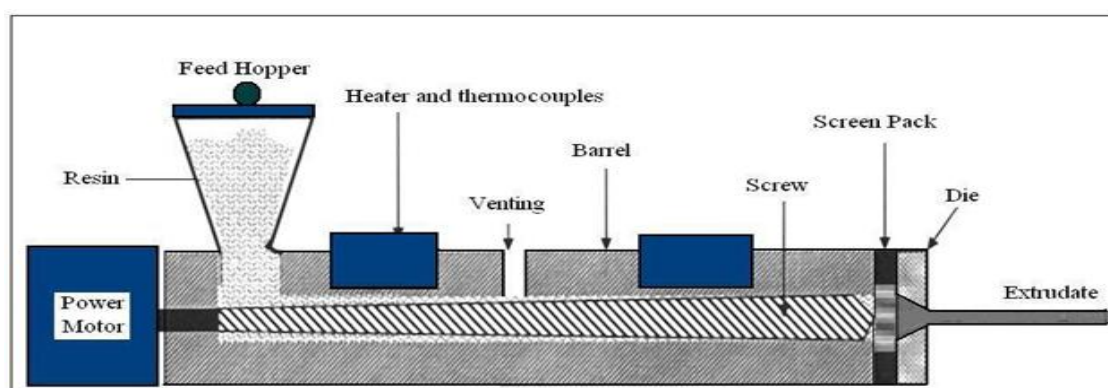


Fig. 4. Schematic diagram representing the components of a single screw melt extruder

#### 4.4 Solvent Evaporation Method

This process generally occurs in two steps. In the first step there is the formulation of a solution in which the matrix material and drug are the major constituents. The second step refers to solvent removal that involves the formation of solid dispersion. The mixing of drug is preferred at the molecular level because it leads to optimal dissolution properties. Then using a suitable process the product is crushed, pulverized and sieved [40].

#### 4.5 Spray-Drying

For solid dispersion preparation spray drying is the most commonly used technique. In this process, drug and carrier are dissolved or suspended and sprayed into the heated airflow steam for the removal of solvent. Then the solvents are quickly evaporated because of large surface area offered by the droplets and within a very short period formation of solid dispersion occurs that may be fast enough for the phase separation. Then the material is air-dried and the product is separated after drying [41].

#### 4.6 Freeze-Drying

In the freeze-drying process firstly the drugs and carriers are dissolved in a common solvent and for the complete frozen it is immersed in the liquid nitrogen. Then this frozen solution is further lyophilized. For spraying the solution firstly the liquid nitrogen nozzle is used. The liquid feed rate and atomizing airflow is then adjusted. The nozzle outlet is then positioned about 10cm above the liquid nitrogen. Then from the jacket of solution hot water is pumped for avoiding the freezing of solution inside the nozzle. Then the formed suspension i.e frozen droplets of solution in liquid nitrogen is transferred to the lyophilizer. As soon as the liquid nitrogen is evaporated the lyophilization process gets started [42, 43].

#### 4.7 Kneading Method

Accurate amount of drug is weighed and carrier mixture is dissolved in it and is wetted insolvent and then it is kneaded continuously in mortar pestle for some time and thus the formed paste is dried and sieved [44].

#### 4.8 Characterization

For identifying the physical nature of solid dispersion number of techniques used are as:

#### 4.8.1 Thermal analysis

##### 4.8.1.1 Thermo-microscopic methods

In the support of DTA and DSC measurement this technique has been applied. This information of binary system-based phase diagram can be achieved using this technique. The observations are recorded by heating the physical mixture or dispersion at the rate of 1-5°C per minute [25].

##### 4.8.1.2 Differential thermal analysis (DTA)

The phase equilibria of pure substance or solid mixture can be effectively studied by differential thermal analysis. In this, the differential heat gets changed by accompanying the physicochemical changes as a function of temperature and thus the substance gets heated at a constant rate. Using this technique the phase diagram is constructed with high reproducibility, for this, a higher temperature is permitted and greater resolution is most real. DTA usually refers to the measurement of the temperature difference between sample and reference material using identical heat treatment. [45]

##### 4.8.1.3 Differential scanning calorimetry (DSC)

In DSC the sample and reference material are both maintained at the same temperature and both are then subjected to linear heating. In this flow of heat which is maintained at isothermal conditions is recorded but the temperature change is not recorded. This method is useful in studying the crystalline behavior and deriving the phase diagram of solid dispersion. As a function of time and temperature DSC is a heat treatment process to find out the flow of heat and temperature related to substance transition [46].

##### 4.8.1.4 X-ray diffraction (XRD)

To detect the crystalline phase in mixed system powder X-Ray diffraction technique is mostly used. However, there are chances of brittleness due to too much crystallinity. There are narrow diffraction peaks in the crystalline part and the broad peak appears in amorphous components. The crystallinity of material can be calculated based on the ratio of two intensities. Single crystal X-ray crystallography generally deals with the study of bond angle and inters atomic distances. Powder x-ray diffraction deals with the parameters involved in the study of crystal lattice; whereas the intensity of x-ray diffraction from the sample is measured concerning the function of

diffraction angle. Thus with the change in the crystal structure the diffraction angle changes. The relationship between x-ray wavelength, the angle of diffraction  $\theta$ , and the distance between atomic planes of crystal latticed of each set is given by the equation:  $M\lambda=2d \sin \theta$ , where M represents the order of diffraction [46].

#### 4.8.2 Fourier transform infrared spectroscopy (FT-IR Spectroscopy)

FTIR spectroscopy is used to study the possible interaction of drugs and polymer in the solid state. The interaction between two compounds and drug degradation can be indicated by peak appearance. Infrared spectroscopy (IR) is mostly used for the detection of variation in energy distribution between the drug and matrix To detect the variation in energy distribution between drug and matrix IR spectroscopy is mostly used. Crystallinity is indicated by sharp vibrational bands. The crystallinity range of 1 to 99 % pure material can be detected by Fourier Transformed Infrared Spectroscopy (FTIR). To follow changes in bonding between the functional group this technique is mostly applied. [47].

#### 4.8.3 Advantages of solid dispersion

1. Solid dispersion is the final stage for reduction of particle size, and there is a moderate dissolution of the drug in the dissolution medium after the addition of a carrier.
2. By using poorly water-soluble drugs and a highly soluble carrier mixture solid dispersion can be used.
3. There is a substantial contribution to the drug solubility enhancement and is related to drug wettability for improvement in solid dispersion. The different carriers having surface activity such as cholic acid and bile salt, leads to an increase in the wettability property of the drug. Thus the carrier leads to influence the drug dissolution profile by direction dissolution or co-solvent effects.
4. In particles the degree of porosity should be higher in solid dispersion. The increase of porosity also depends upon the carrier properties.

5. By incorporating the anticancer drug in solid dispersion bioavailability has been found to be improved [48].

#### 4.8.4 Disadvantages of solid dispersions

Instability is the major cause of disadvantages in solid dispersion.

1. The amorphous state may undergo crystallization during the purifying (mechanical stress) or storage (temperature and humidity stress) hence this is not widely used in marketed products.
2. Sometimes there may be chances of phase separation, crystal growth, or conversion of amorphous form to crystalline form or metastable form during the storage because in solid dispersion most of the polymer leads to absorption of moisture. Because of this reason, the solubility and dissolution rate of the drug may be decreased. [48,49]

#### 4.8.5 Application of solid dispersion

Solid dispersion can provide various benefits some of them are as:

1. During the lungs transplantation of patients for improving the immunosuppressive therapy solid dispersion containing dry powder is prepared for inhalation therapy. Many problems such as the use of local anesthesia and irritating solvents can be improved by this technique.
2. For accelerating the quick onset of action solid dispersion drugs have been demonstrated such as non-steroidal anti-inflammatory drugs (NSAID) where the immediacy of action is crucial in relieving acute pain and inflammation.
3. Solid dispersion have been used to provide a bioavailable oral dosage form for anticancer drugs, that could be used in place of injections for improving patient compliance & comfort. [28,33,42,49].

**Table 2. Some of the solid dispersion technique for solubility enhancement [35,10,14, 7, 50]**

S.NO	Name of Formulation	Technique Used
1	Etoricoxib and Poloxomer 188 Solid dispersion	Kneading
2	Etoricoxib and Poloxomer 188 Solid dispersion	Physical Mixture
3	Cinnarizine and PVP K30 Solid dispersion	Kneading
4	Cinnarizine and Ploxomer 188 Solid dispersion	Physical Mixture

**Table 3. Marketed formulation of solid dispersion [50]**

S.NO	Product Name	Drug	Polymer	Technique	Maximum Drug Loading Per Tablet/Capsule (mg)	Dosgae Form
1	Kalydeco	Ivacaftor	HPMC	Spray Drying	150	Tablet
2	Zelboraf	Vemurafenib	HPMC	Coprecipitation	240	Tablet
3	Incivek	Telaprevir	HPMC	Spray Drying	375	Tablet
4	Intelence	Etavirine	HPMC	Spray Drying	200	Tablet
5	Novir	Ritonavir	PVP	Melt Extrusion	100	Tablet
6	Kaletra	Lopinavir	PVP	Melt Extrusion	200	Tablet

#### 4.8.6 Suitability of polymer and selection of method based on properties of drugs [51,52,53]

There are different categories of polymers used for solubility enhancement techniques such as Poloxamer 188, PVP K30, HPMC, etc. The polymer must be compatible with the drug and must not degrade at given temperature and humidity conditions.. There are different techniques used in the solubility enhancement technique. The selection of method is based on a technique that leads to solubility improvement, improvement of dissolution rate, and hence the bioavailability of the poorly water-soluble drug, solid dispersion having higher dissolution rates can be employed to several factors that include:

- It leads to the formation of metastable states of components having higher energy as a function of the carrier system and can be used in the proportions of carrier present.
- It leads to particle size reduction equal to the molecular level.
- As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles leading to an increase in both surface area and solubilization for fast dissolution and absorption
- Can be used in the formation of amorphous forms of drugs and carriers.

The aggregation of fine particles can be prevented by the presence of carriers, thus providing a large surface area for drug dissolution. Because of the surfactant properties of polymer the wetting properties of drugs are also increased. The presence of carriers leads to inhibiting the crystal growth that will facilitate faster dissolution. Various types of excipients having aqueous solubility were used as carriers of solid solution/dispersion. Few of them, as polyethylene glycols (PEG, Mw 1500-20000) is

used mostly because of good solubility in aqueous and organic solvents, having a low melting point (under 65°C) and have the properties of solubilizing various compounds and thus improve the wettability of compound.

For example, the marketed formulation of solid dispersion of griseofulvin in PEG 8000 is Gris-PEG. Polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyvinyl pyrrolidone polyvinyl acetate copolymer (PVP-PVA), hydroxyl propyl methylcellulose (HPMC), hydroxyl propyl cellulose (HPC), urea, Poloxamer 407, sugars, emulsifiers (SDS, Tween 80), and organic acids (succinic acid and citric acid) are some other substances which are used as carriers in solid dispersion preparation. Since the water-soluble carriers are having faster dissolution as compared to the drug, hence the drug-rich layers were formed on the surface of dissolving plugs that prevent the continuous dissolution of the drug in the solid dispersion. Therefore, surface-active or self-emulsifying agents such as bile salts, lecithin, lipid mixtures, Gelucire 44/14, and Vitamin E TPGS NF were employed as additional additives, thus preventing the formation of the insoluble aqueous surface layer by acting on dispersion or emulsifying carrier. In addition by using the aqueous insoluble carriers, the release behavior of many drugs is found to be improved, as crospovidone and enteric polymers such as hydroxyl propyl methyl cellulose (HPMCP), cellulose acetate phthalate (CAP), Eudragit L 100 and S100, and Eudragit E3.

## 5. CONCLUSION

To attain the desired concentration or the therapeutic response in orally administered drug solubility is one of the rate-limiting parameters. For the formulation, scientist solubility is the major challenge. In this review, the solid dispersion technique has been described that can be successfully used to enhance the solubility of hydrophobic drugs and can be used



either alone or in combination for enhancing the oral bioavailability, but the improvement in solubility and bioavailability depends upon the selection of method. Among all the solubility enhancement techniques solid dispersion technique is the most commonly used and most acceptable technique for solubility enhancement because of its easiness, cost-effectiveness and maximum solubility enhancement over other techniques.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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