A REVIEW: SOLID DISPERSION

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ABSTRACT
The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The various techniques are available for enhancement of solubility. Solid dispersion is one of the most promising approaches for solubility enhancement. Currently only 8% of new drug candidates have both high solubility and permeability. More than 60% of potential drug products suffer from poor water solubility. In solid dispersion particle size of drug is reduced or a crystalline pure drug is converted into amorphous form and hence the solubility of drug is increased. Polymers incorporated in solid dispersion technologies are usually hydrophilic in nature and also showing compatibility with the drug to enhance the drug solubility. The present article reviews the basic concept about solid dispersion, various types of solid dispersion, criteria of solvent selection, the methods of preparation, characterization, their advantages, limitations, applications, future prospect and various types of marketed preparations.

Key Words: Solubility, Hydrophilic, Fusion method, Carrier, Solid Dispersion, Polymer.

INTRODUCTION
Many potential drug candidates are characterized by a low oral bioavailability. Often poor drug dissolution/solubility rather than limited permeation through the epithelia of the gastrointestinal tract are responsible for low oral bioavailability. The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate of extent of absorption of the drug. When an active agent given orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, 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 focus on improving the
oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs.\textsuperscript{[2]} The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.\textsuperscript{[3]} There are various techniques such as, particle size reduction, micronization, physical modifications, nano suspension, modification of crystal habit such as, polymorphs, pseudo polymorphs, complexation, solubilization, salt formation, and use of cyclodextrins which can enhance the solubility & dissolution rate of insoluble drug but this techniques having some practical limitations, solid dispersion technique overcome this practical limitations. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. Solid dispersion technique can be used to enhance the solubility; dissolution rate and absorption of several insoluble drugs\textsuperscript{[4]}. The term solid dispersion refers to group of solid products consisting of at least two different components, generally a hydrophilic matrix and hydrophobic drugs.\textsuperscript{[5]} There are various techniques available to improve the solubility of poorly soluble drugs, such Micronization, Nanosuspension, Modification of the crystal habits, Eutectic mixtures, Solid dispersions, Micro emulsions, Self micro emulsifying drug delivery systems, cyclodextrin inclusion and lipid based delivery systems etc. This review focuses on the solid dispersion technique of solubilization for the attainment of effective absorption and improved bioavailability. Solid dispersion is one of the most promising approaches for solubility enhancement. 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. In case of solid dispersion drug disperse in the matrix generally a hydrophilic matrix and a hydrophobic drug, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs\textsuperscript{[6]}.

**SOLID DISPERSION**

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release
of drugs, altered solid state properties, enhanced release of drugs from ointment and suppository bases, and improved solubility and stability \[7\].

**TYPES OF SOLID DISPERSION \[8\]**

(A) **Eutectic Mixtures**

When a mixture of A and B with composition E 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. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

(B) **Solid Solutions**

According to their miscibility two types of solid solution are

**Continuous Solid Solutions**

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

**Discontinuous Solid Solutions**

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram shows the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease.

**Substitutional Crystalline Solutions**

A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which the solute molecules substitute for 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.

Interstitial Crystalline Solid Solutions
In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

(C) Amorphous Solid Solutions
In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers urea and sugars such as sucrose, dextrose and galactose, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol and various cellulose derivatives have been utilized for this purpose.

(D) Glass Solutions and Glass Suspensions
A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature.

Selection of A Carrier
A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.
1. Freely water-soluble with intrinsic rapid dissolution properties.
2. Non-toxic and pharmacologically inert.
3. Heat stable with a low melting point for the melt method.
4. Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
5. Able to preferably increase the aqueous solubility of the drug and
6. Chemically compatible with the drug and not form a strongly bonded complex with the drug.

**First generation carriers**
Example: Crystalline carriers: Urea, Sugars, Organic acids \[^{10}\].

**Second generation carriers**
Example: Fully synthetic polymers include povidone (PVP), polyethylene glycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins \[^{11}\].

**Third generation carriers**
Example: Surface active self emulsifying carriers: Poloxamer 408, Tween80, and Gelucire 44/14 \[^{12}\].

**In Vitro Dissolution study**
Dissolution studies were performed in phosphate buffer (pH 7.2, 900 ml) at 37 ± 0.5 °C, using USP XXIII apparatus with a paddle rotating at 50 rpm. The samples equivalent to 100 mg ibuprofen, were added in vessel containing phosphate buffer. At fixed time intervals, samples (5 ml) were withdrawn and equal amount of fresh dissolution medium was added. The samples were filtered through 0.45 μm membrane filter, and analyzed by UV-VIS spectrophotometer (shimadzu Corporation, Japan) at 222 nm wavelength. \[^{13,14}\].

**In-vivo Study**
The anti-inflammatory activity of optimized preparation of solid dispersion & marketed preparation was carried out using three groups each containing two rat animals. One group for control, second group for marketed preparation & third group for optimized solid dispersion was used. 0.1 ml of 1% carageenan was injecting in the sub plantar region of left hind paw of each animal of each group. After 15 minutes of carageenan administration initial swelled area of left hind paw were measured by plethysnometer. Then marketed preparation and solid dispersion containing Ibuprofen were injected subcutaneously to second and third group respectively. The swelled area was measured by plethysnometer. \[^{15}\].

**Classification of solid dispersions**: The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles by melting or solvent method. Therefore, based
on their molecular arrangement, different types of solid dispersions (SDs) can be distinguished. They are described in Table 1\textsuperscript{16}

**Table 1: Types of solid dispersions**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Solid dispersion type</th>
<th>Matrix *</th>
<th>Drug **</th>
<th>Remarks No.</th>
<th>Phases</th>
<th>Ref. to lit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Eutectics</td>
<td>c</td>
<td>c</td>
<td>First type of solid dispersion prepared</td>
<td>2</td>
<td>(Chiou and Riegelman, 1971)</td>
</tr>
<tr>
<td>2.</td>
<td>Amorphous precipitations in crystalline matrix</td>
<td>C</td>
<td>A</td>
<td>Rarely encountered</td>
<td>2</td>
<td>(Breitenbach AH, 2002); (Mullins and Macek, 1960)</td>
</tr>
<tr>
<td>3.</td>
<td>Solid solutions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>Continuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>Miscible at all composition, never prepared</td>
<td>1</td>
<td>(Goldberg et al., 1965)</td>
</tr>
<tr>
<td>ii</td>
<td>Discontinuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>Partially miscible, 2 phases even though drug is molecularly dispersed</td>
<td>2</td>
<td>Sekiguchi K and Obi N (1961)</td>
</tr>
<tr>
<td>iii</td>
<td>Substitutional solid solutions</td>
<td>C</td>
<td>M</td>
<td>Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or dis-continuous. When discontinuous: 2 phases even though drug is molecularly dispersed.</td>
<td>1 or 2</td>
<td>(Rastogi and Verma, 1956); (Wilcox et al., 1964)</td>
</tr>
<tr>
<td>4.</td>
<td>Interstitial solid solutions</td>
<td>C</td>
<td>M</td>
<td>Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous.</td>
<td>2</td>
<td>(Chiou and Riegelman, 1971); (Chiou and Riegelman, 1969)</td>
</tr>
<tr>
<td></td>
<td>Example: Drug in helical interstitial spaces of PEG.</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Glass suspension</td>
<td>A</td>
<td>C</td>
<td>Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix</td>
<td>2</td>
<td>(Chiou and Riegelman, 1971); (Sarkari M et al., 2002)</td>
</tr>
<tr>
<td>6.</td>
<td>Glass suspension</td>
<td>A</td>
<td>A</td>
<td>Particle size of dispersed phase dependent on cooling/evaporation rate. Many solid dispersions are of this type</td>
<td>2</td>
<td>(Chiou and Riegelman, 1971); (Sarkari M et al., 2002)</td>
</tr>
<tr>
<td>7.</td>
<td>Glass solution</td>
<td>A</td>
<td>M</td>
<td>Requires miscibility OR solid solubility, complex formation upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP</td>
<td>1</td>
<td>Simonelli AP et al., 1969</td>
</tr>
</tbody>
</table>

* A: matrix in the amorphous state, C: matrix in the crystalline state  
** A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix

**Advantages of Solid Dispersion**[^17,18]

Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. The ultimate result is improved bioavailability. Wettability is improved during solid dispersion production. Improved wettability results in increased solubility. Here the carriers play the major role to improve the wettability of the particles. Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties.
In solid dispersions drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles. Rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in presystemic both can lead to the need for lower doses of the drug.

**Disadvantages of Solid Dispersion**[^18]

The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, AbbVie) from the market. Moisture and temperature have more of a deteriorating effect on solid dispersions than on physical mixtures. Some solid dispersion may not lend them to easy handling because of tackiness.

**Mechanism of Increased Dissolution Rate**[^19]

The main reasons postulated for the observed improvements in dissolution of these systems are as follows

**a) Reduction of particle size**

In case of glass, solid solution and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to an increase in both the surface area solubilization.

**b) Solubilization effect**

The carrier material, as it dissolves may have a solubilization effect on the drug. This was shown to be the case for acetaminophen and chlorpropamide in urea as well as for numerous other drugs.

**c) Wettability and dispersibility**

The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media. This should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.
d) Metastable Forms

Formation of metastable dispersions with reduced lattice energy would result in faster dissolution rates. It was found that the activation energies for dissolution for furosemide was 17 K Cal per mol, whereas that for 1:2 furosemide: PVP coprecipitate was only 7.3 K Cal per mol.

CHARACTERIZATION OF SOLID DISPERSION

Many methods are available that can contribute information regarding the physical nature of solid dispersion system. A combination of two or more methods is required to study its complete picture \(^{[20]}\).

- Thermal analysis.
- Spectroscopic method.
- X-ray diffraction method.
- Dissolution rate method.
- Microscopic method.
- Thermodynamic method.
- Modulated temperature differential scanning calorimetry
- Environmental scanning electron microscopy
- Dissolution testing

Recent Advances And Future Trends: Solid dispersion has great potential both for increasing the bioavailability of drug and developing controlled release preparations. Thus, to solve bioavailability issues with respect to poorly water-soluble drugs, solid dispersion technology has grown rapidly. The dosage form can be developed and prepared using small amounts of drugs substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation

Table 2: List of poor water soluble drugs, Category & Solubility profile\(^{[21]}\)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Category</th>
<th>Solubility profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ibuprofen</td>
<td>Anti-inflammatory analgesic</td>
<td>Ibuprofen is only very slightly soluble in water. Less than 1 mg of ibuprofen dissolves in 1 ml water (&lt; 1 mg/mL). However, it is much more soluble in alcohol/water mixtures</td>
</tr>
<tr>
<td>No.</td>
<td>Drug</td>
<td>Category</td>
<td>Solubility Details</td>
</tr>
<tr>
<td>-----</td>
<td>---------------</td>
<td>-----------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2</td>
<td>Furosemide</td>
<td>Diuretics</td>
<td>Soluble in acetone, sparingly soluble ethanol (95%), slightly soluble in ether</td>
</tr>
<tr>
<td>3</td>
<td>Gliclazide</td>
<td>Anti diabetic</td>
<td>Sparingly soluble in dichloromethane, slightly soluble in ethanol 95%.</td>
</tr>
<tr>
<td>4</td>
<td>Glipizide</td>
<td>Anti diabetic</td>
<td>Soluble in ether, sparingly soluble ethanol (95%), slightly soluble in acetone</td>
</tr>
<tr>
<td>5</td>
<td>Aceclofenac</td>
<td>Anti inflammatory, analgesic</td>
<td>Practically insoluble in water; freely soluble in dichloromethane, slightly soluble in ethanol 95%.</td>
</tr>
<tr>
<td>6</td>
<td>Indometacin</td>
<td>Anti-inflammatory, analgesic</td>
<td>Soluble in chloroform sparingly soluble in ethanol 95%</td>
</tr>
<tr>
<td>7</td>
<td>Ketoprofen</td>
<td>Anti-inflammatory, analgesic</td>
<td>Freely soluble in ethanol 95%, chloroform, and ether</td>
</tr>
<tr>
<td>8</td>
<td>Diclofenac</td>
<td>Anti-inflammatory</td>
<td>Freely soluble in methanol, Soluble in ethanol (95%), Sparingly soluble in water and glacial acetic acid.</td>
</tr>
<tr>
<td>9</td>
<td>Felodipine</td>
<td>Calcium Channel blocker</td>
<td>Sparingly soluble in dichloromethane, slightly soluble in ethanol 95%</td>
</tr>
<tr>
<td>10</td>
<td>Ioperamide</td>
<td>Antidiarrheals</td>
<td>Soluble in acetone, sparingly soluble ethanol (95%), slightly soluble in ether</td>
</tr>
<tr>
<td>11</td>
<td>Morphine</td>
<td>NSAIDS</td>
<td>Soluble in water, Freely soluble in hot water, More soluble in hot ethanol</td>
</tr>
<tr>
<td>12</td>
<td>Naproxone</td>
<td>Anti-inflammatory</td>
<td>Soluble in water, Freely soluble in hot water, More soluble in hot ethanol</td>
</tr>
<tr>
<td>13</td>
<td>Nimodipine</td>
<td>Calcium channel blocker</td>
<td>Poor water soluble drug</td>
</tr>
<tr>
<td>14</td>
<td>Ofloxacin</td>
<td>Antibiotic</td>
<td>Soluble in ethanol and chloroform, Insoluble in ether.</td>
</tr>
</tbody>
</table>

**Selection of the Carrier**

The selection of the carrier has the influence on the dissolution characteristics of the dispersed drug, since the dissolution rate of one component from the surface is affected by the other component in a multiple component mixture. Therefore, a water-soluble carrier results in a faster release of the drug from the matrix. A poorly soluble or insoluble carrier leads to slower release of a drug from the matrix. If the active drug present is a minor component in the dispersion, faster release of a drug can be achieved from matrix. [22]

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug. [23,24,25,26]
- Freely water-soluble with intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert.
- Heat stable with a low melting point for the melt method.
- Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
- Able to preferably increase the aqueous solubility of the drug.
- Chemically compatible with the drug and not form a strongly bonded complex with the drug.

**FIRST GENERATION CARRIERS**
Example: Crystalline carriers: Urea, Sugars, Organic acids\(^{[27]}\).

**SECOND GENERATION CARRIERS**
Example: Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates\(^{[23]}\). Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins\(^{[25]}\).

**THIRD GENERATION CARRIERS**
Example: Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/141

The Classification of solid dispersion is given blow in the figure 1

![Classification of Solid Dispersion](image-url)
Methods of solid dispersion

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) technology

1. Fusion method

The melting or fusion method is the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melts. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures. However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier. The main advantages of this method are its simplicity and economy. The disadvantages are: i) that the method is only applied when the drug and matrix are compatible and when they mix well at the heating temperature. When the drug and matrix are incompatible two liquid phases or suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion and this problem can be prevented by using surfactants. ii) Another problem may arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug
occurred, whereas fast cooling yielded amorphous solid dispersions. iii) Many substances, either drugs or carriers, may decompose during the fusion process at high temperatures.\textsuperscript{[29-30]}

2. Solvent method

The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, using the solvent method the pharmaceutical engineer faces two challenges. The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution. Low drug concentrations are used to dissolve both drug and matrix material in water, but this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical. Solubilizers like cyclodextrins or surfactants like Tween80® increase the aqueous solubility of the drug substantially. However, the amounts of solubilizers or surfactants in the final product are often eminent. Moreover, only dosage forms with low drug loads are possible. In addition, they are not always tolerated well in the body or may even be toxic. The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s). Drying at high temperatures speeds up the process and reduces the time available for phase separation. On the other hand, at high temperatures the molecular mobility of drug and matrix remains high, favoring phase separation (e.g., crystallization). To dry the solutions, vacuum drying moderate heating is often used. Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. Afterwards the formed solid dispersion is often stored in vacuum desiccators to remove the residual solvent. Another drying technique is spray drying. For these reasons, hot melt extrusion is the current method of choice for the preparation of solid dispersions.\textsuperscript{[29,31,32]}

3. Melting solvent method (melt evaporation)

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is
then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5–10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg and particularly useful for drugs that are thermolabile or have high melting points.\textsuperscript{[29,33]}

4. Melt extrusion method

Hot-stage extrusion (HME) consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed. The concentration of drug in the dispersions is always 40% (w/w). Samples are milled for 1 min with a cutting mill and sieved to exclude particles >355 μ. A reduction in processing temperature can be achieved by the association of hot-stage extrusion with the use of carbon dioxide as a plasticizer which broadens the application of hot-stage extrusion to thermally labile compounds. HME also offers several advantages over traditional pharmaceutical processing techniques including the absence of solvents, few processing steps, continuous operation, and low temperature, short residence time which prevents the drug-carrier mixture from thermal degradation, more possibility of the formation of solid dispersions and improved bioavailability. This method has several disadvantages these are: (i) high shear forces may produce high local temperature in the extruder therefore it may create a problem for heat sensitive materials, (ii) just like traditional fusion method, miscibility of drug and carrier matrix can be a problem. Some examples of pharmaceutically approved polymeric materials which are used in hot-melt extrusion include vinyl polymers [polyvinylpyrrolidone (PVP), PVP-vinyl acetate (PVP-VA)], polyethylene oxide (PEO), Eudragit\textregistered (acrylates), Polyethylene glycol (PEG) and cellulose derivatives.\textsuperscript{[30,32]}
5. Lyophilization Technique (Freeze-drying)
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. This technique was proposed as an alternative technique to solvent evaporation. The advantages of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized as soon as the solution is vitrified. An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent results in even faster vitrification, thereby decreasing the risk for phase separation to a minimum. Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary or nasal administration. [30,32]

6. Melt Agglomeration Process: This technique has been used to prepare solid dispersion wherein the binder acts as a carrier. In addition, solid dispersions are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt-in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersion by melt agglomeration. It has been found that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles. [29]

7. The use of surfactant
The utility of the surfactant systems in solubilization is very important. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floating, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants
have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.\(^{[29]}\)

8. Electrospinning
Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulate on the surface of a pendant drop; destabilize the hemispherical shape into a conical shape (commonly known as Taylor’s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The thinning down of the charged jet is limited. If the viscosity increases, the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.\(^{[29,32]}\)

9. Super Critical Fluid (Scf) Technology
The supercritical fluid antisolvent techniques, carbon dioxide are used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system, precipitation with a compressed fluid antisolvent, gas anti-solvent, solution enhanced dispersion by supercritical fluids and supercritical antisolvent. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5-2,000nm in diameter. The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently. Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon
dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. [29,32]

**Preparation of Solid Dispersions**

Various methods are used for preparation of solid dispersion system. These methods are depicted in figure 2. [29]

![Diagram of solid dispersion methods](image)

**CONCLUSION**

The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Dissolution of drug is the rate determining step for oral absorption of drugs which can subsequently affect the in vivo absorption of drug. So to improve the aqueous solubility of the drugs, many techniques have been adopted since decades and solid dispersion is one of those techniques. Use of solid dispersions for the development of the release rate and oral bioavailability of poorly water soluble drugs, by careful choice of the carrier it is also feasible to delay or slow down the release pattern of a drug by formulating it into solid dispersion.
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