Review article

Strategies to Enhance Solubility and Dissolution of a poorly water soluble drug


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Abstract
Solid dispersion is used for enhancing dissolution rate of a therapeutically active substance and in turns its absorption and in vivo efficacy. Solid dispersion is generally prepared with drug which is having poor aqueous solubility and hydrophilic carrier. Generally polyethylene glycol, polyvinyl pyrrolidone, mannitol, urea, gums, eudragit are used as hydrophilic carriers. Certain hydrophilic swellable polymers sodium carboxy methyl cellulose, pregelatinized starch, sodium starch glycolate are also used. Sometimes surfactant is also added to further improve wetting property of solid dispersion. 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. Solid dispersion is not only used in improving dissolution rate of poorly water soluble drug but also in masking the taste of the drug substance, preparing rapid disintegration oral tablets and in producing sustained release microspheres. Various methods are available to prepare solid dispersion generally solvent evaporation method, melting method, melt solvent method, kneading method, co-grinding method, co-precipitation method, modified solvent evaporation method, spray drying, gel entrapment technique, co-precipitation with supercritical fluid. Evaluations of solid dispersion are done by Fourier Transform infra- red spectroscopy, X-Ray diffractometry, scanning electron microscopy, differential scanning calorimetry, solubility and dissolution experiments.

Key words: solid dispersion, hydrophilic carrier, dissolution, desiccators, FT-IR, Spectroscopy, DSC.

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1. Introduction

Poor aqueous solubility of drugs is major limiting factor with many new drugs in their successful launch in market inspite of their potential pharmacokinetic activity. About 90% of all compounds in today’s pharmaceutical drug delivery pipelines are reported to be poorly soluble in water. This process enormous problem for the industry; for an active pharmaceutical ingredients cannot reach its molecular target in the body if the drug remains undissolved in the gastrointestinal tract [GIT] and is eventually excreted. The massage simple:
drugs that don’t dissolve will not heal you. Therefore poor solubility is critical factor if the molecule is to survive the pharmaceutical development process. Even those molecules that would have highly beneficial effect on their physiological target would not be further developed if their bioavailability is limited by their solubility in water. Further poorly water soluble drugs are generally administered at much higher dose than the actual dose in order to achieve necessary drug plasma level leading to improved adverse reaction and cost of therapy and often yields erratic pharmacological response and hence poor patient complains. In addition, the manufacturing cost would increase since a large amount of active pharmaceutical ingredient (API) might be consumed to develop and manufacture the drug product [1].

Thus solubilisation technologies that overcome this issue by increasing the solubility of such drug candidates are becoming more and more important to the pharmaceutical industry by opening pathway to prepare effective and marketable drugs from active that would otherwise useless [2].

**Solubility**

The term ‘solubility’ is defined as maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water [3].

**Possible Causes for Poor Oral Absorption**

Any drug is said to be poorly soluble when:

- Aqueous solubility <100μg/ml
- High crystal energy (melting point >2000 C)
- Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm2/min
- High molecular weight: (>500), Self association and aggregation.

**Table 1. Definitions of solubility [4]**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Parts of solvent required for one part of solute</th>
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</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>1 – 10</td>
</tr>
<tr>
<td>Soluble</td>
<td>10 – 30</td>
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<tr>
<td>Sparingly soluble</td>
<td>30 – 100</td>
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<tr>
<td>Slightly soluble</td>
<td>100 – 1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>1000 – 10,000</td>
</tr>
<tr>
<td>Insoluble</td>
<td>&gt; 10,000</td>
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</tbody>
</table>

**Process of Solubilation [5]**

The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion [7].

**Step 1:** Holes opens in the solvent
Step 2: Molecule of the solid breaks away from the bulk

Step 3: The feed of solid molecule is integrated into the hole in Solvent.

Figure 1. Process of solubilisation

Factors Affecting Solubility [2, 6]

Temperature
Temperature will affect solubility. If the solution process absorbs energy then the temperature is increased as the solubility will be increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

Pressure
For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

Nature of the solute and solvent: While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their natures.

Particle Size
The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by:

$$\log \frac{S}{S_0} = \frac{2}{2.303 R T} \gamma \frac{V}{r}$$

Where, S is the solubility of infinitely large particles
S0 is the solubility of fine particles
V is molar volume
γ is the surface tension of the solid
r is the radius of the fine particle
T absolute temperature in degree Kelvin
R universal gas constant

Molecular size
The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

Polymorphs
A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A
crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropy. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

**Polarity**

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules.

**Selection Criteria of Drug [7-10]**

The Biopharmaceutics Classification System (BCS) was introduced by US food and Drug Administration (FDA) to assess oral drug product. In this system, drug are classified into four groups based on the ability of a given drug substance to permeate biological membranes and aqueous solubility. A given drug substance is considered ‘highly soluble’ when the highest dose strength is soluble in 250 ml water or less over pH range 1 to 7.5, and is considered ‘highly permeable’ when extent of absorption human is determined to be ≥90% of an administered dose (in solution), based on mass balance or related to an intravenous reference dose. For rapidly dissolving tablet, ≥85% of the labelled amount of drug substance must dissolved in 30 minutes [8].

According to BCS system, drug are classified into four groups are as follows [11].

**Class I** consist of highly water-soluble drug that are well absorbed from the gastrointestinal tract and in general, have the preferred physicochemical properties drug in Class I have high bioavailability after oral administration.

**Class II** consist of water-insoluble drug that, when dissolved, are well absorbed from gastrointestinal tract. The dissolution rate in-vivo is usually the rate-limiting step in drug absorption. Commonly drugs in this class have variable absorption due to numerous formulation effects and in-vivo variable that can be affect their dissolution profile.

**Class III** consists of water-soluble drugs that do not permeate biomembranes readily.

**Class IV** consist of water-insoluble drug that, when solubilised, do not permeate biomembrane readily. Unfortunately most
new chemical entities are water-insoluble lipophilic compound or in other words Class II or even Class IV compounds. It can be quite challenging for the formulation scientist to develop usable pharmaceutical product from such compound. Recently group of complexing agent called 'cyclodextrin' and other water soluble polymers have been included in to formulator’s armamentarium. Solid dispersion method is one of the effective approach to achieve this ideal goal particularly for the drug with poor aqueous solubility in which the drug incorporated in to water soluble matrix. Today 40% of all new chemical entities suffers from the poor aqueous solubility. It generally recognized that low solubility or dissolution rate often become rate limiting step in absorption of poorly water soluble drug from gastrointestinal tract and compromise oral bioavailability. Chiou and Riegelman defined the term solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carrier by melting of their physical mixture” [12].

**Techniques to Overcome Poor Solubility [13-16]**

The description of a technology as 'solubility enhancing' can be misleading, since although the phenomenon of supersaturation is real, the techniques used do not increase the solubility of insoluble compounds. More accurately, they present the drug in a form which is optimal to its absorption, given its solubility limitations. It is also important to be aware that water solubility also requires the specification of temperature and pH; many important drugs only exhibit aqueous solubility under certain physiological conditions, and these need to be meet at the site of absorption. This topic focuses on the technologies that have arisen to meet the challenge posed by insoluble compounds and the ways in which these technologies have made a difference. The techniques that are used to overcome poor drug solubility are discussed under following major headings.

**I. Chemical Modifications:**

1. Salt Formation
2. Co-crystallization
3. Co-solvency
4. Hydrotropic
5. Solublizing agent
6. Nanotechnology

**II. Physical Modifications:**

1. Particle size reduction
   a. Micronization
   b. Nanosuspension
2. Modification of the crystal habit
   a. Polymorphs
   b. Pseudopolymorphs
3. Complexation
   a. Use of complexing agents
4. Solubilization by surfactants
   a. Microemulsions
   b. Self microemulsifying drug delivery system
5. Drug dispersion in carriers
   a. Solid dispersions
   b. Solid solutions

**I. Chemical Modifications**

1. Salt formation: is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Ex. Aspirin, Theophylline, Barbiturates.

2. Co-crystallisation: New approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. A co-crystals may be defined as crystalline material that consist of two or more molecular (and electrical neutral) species held together by non-covalent forces. It can be prepared by evaporation
of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt and slurry preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds.

3. Co-solvent: It is well-known that the addition of an organic co-solvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. Solvent used to increase solubility known as co-solvent. It is also commonly referred to as solvent blending.

4. Hydrotropy: It designates to increase in solubility in water due to presence of large amount of additives. It improves solubility by complexation involving weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, urea) and solute. Ex. Sublimation of Theophylline with Sodium acetate and Sodium alginate.

5. Solubilising agents: The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. PEG 400 is improving the solubility of hydrochlorothiazide.

6. Nanotechnology approaches: Nanotechnology will be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometres (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has very low effective surface area for dissolution and next step taken was nanonisation [17].

II. Physical Modifications

1. Particle size reduction: The techniques of size reduction using various milling processes are well established and these practices are a standard part of formulation development. This can be done mainly by Micronization and Nanosuspension. As particle size decreases, surface area of particle increases resulting in increase in solubility. Sometimes Sonocrystallisation technique is also used for particle size reduction.

2. Modification of crystal habit: Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability. Similarly amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase in surface area. Order for dissolution of different solid forms of drug Amorphous >Metastable polymorph >Stable polymorph

3. Complexation: Complexation is the association between two or more molecules to form a non bonded entity with a well defined stichometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Ex. of complexing agents are; chelates- EDTA, EGTA, molecular complexes- polymers, inclusion complexes cyclodextrins.

4. Solubilisation by surfactants:
Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or non-ionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension but increases solubility of drug within an organic solvent.

**Solid Dispersion Technology [13-16]**

**Introduction to 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. The enhancement of oral bioavailability of a poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilisation and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the GIT may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilisation of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate/prepare solid dispersion. Solid dispersion of an amorphous drug in a polymer matrix has been demonstrated to be an effective tool for solubility and subsequently bioavailability enhancement.

In 1961, Sekiguchi and Obi [18] developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome, which was termed as “Solid Dispersion”

**Figure 3. A schematic representation of the bioavailability enhancement of a poorly water soluble drug by solid dispersion**
compared with conventional tablet or capsule.

The advantage of solid dispersion compared with conventional capsule or tablet formulations is shown schematically in Figure 3 [19]. From conventional capsules and tablets, the dissolution rate is limited by the size of the primary particles formed after the disintegration of dosage forms. In this case, an average particle size of 5µm is usually the lower limit, although higher particle sizes are preferred for ease of handling, formulation and manufacturing. On the other hand, if a solid dispersion or a solid solution is used, a portion of the drug dissolves immediately to saturate the gastrointestinal fluid, and the excess drug precipitates out as fine colloidal particle or oily globules of submicron size. Because of such easily promises in the bioavailability enhancement of poorly water-soluble drugs, solid dispersion has become one of the most active areas of research in the pharmaceutical field.

Types of solid dispersions [20]

a. Simple eutectic mixture: An eutectic mixture of a sparingly water soluble drug and a highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component. The increase in surface area is mainly responsible for increased rate of dissolution. This led to a conclusion that the increase in dissolution was mainly due to decreased particle size.

b. Solid solutions: Solid solutions consist of a solid solute dissolved in a solid solvent. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems.

c. Glass solution of suspension: A glass solution is a homogenous system in which a glassy or a vitreous of the carrier solubilizer drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent.

d. Compound or complex formation: This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of the drug from the complex is dependent on the solubility dissociation constant and the intrinsic absorption rate of the complex.

e. Amorphous precipitation: Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.

Applications of solid dispersions [21]

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 (up to 10%) 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.
7) Polymorphs in a given system can be converted into isomorphous, solid
solution, eutectic or molecular addition compounds.

**Advantages of solid dispersion [22]**

- It has rapid dissolution rates.
- Increases absorption rate of drugs.
- To decrease the crystalline structure of drug in to amorphous form.
- To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
- To mask the taste of the drug substance.
- To prepare rapid disintegration oral tablets.
- Inhibition of enzymes by the carrier i.e. avoid degradation or decomposition of drugs.
- Transformation of the liquid form of the drug into a solid form (Ex. Clofibrate and Benzoyl benzoate can be incorporated into PEG-6000 to give a solid).
- Avoidance of polymorphic changes and thereby bioavailability problems, (as in the case of nabilone and PVP dispersion and protection of certain drugs by PEGs (Ex. cardiac glycosides) against decomposition by saliva to allow buccal absorption.

**Disadvantages of solid dispersion [22]**

- Instability of solid dispersion.
- It shows crystallinity and decrease in dissolution rate with aging.
- Moisture and temperature have deteriorating effect on solid dispersion.

**Limitations of solid dispersion system [22]**

Despite extensive expertise with solid dispersions, there are some problems which limit the commercial application of solid dispersions.

1) The primary reasons is the poor predictability of solid dispersion behavior due to a lack of a basic understanding of their material properties.

2) There is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also of a vital concern, because it may increase drug mobility and promote drug crystallization.

3) Most of the polymers used in solid dispersions can absorb moisture, which may result in the phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate.

**Mechanism of Increased Dissolution Rate [23-24]**

The enhancement in dissolution rate as a result of solid dispersion formulation, relative to pure drug varies from as high as 400 folds to less than two-fold. Corrigan reviewed the current understanding of the mechanism of release from solid dispersion. The increase in dissolution rate for solid dispersion can be attributed to a number of factors. It is very difficult to show experimentally that any one particular factor is more important than another. 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.

**Methods of Preparing Solid Dispersions [21,23,25]**

Various techniques have been taken in to consideration for manufacturing of solid dispersion and these techniques deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible and during the preparation, de-mixing (partially or complete), and formation of different phases is observed. This phase separation can be controlled by some approaches that have been given in one of the first studies on solid dispersion and they can be briefly described as follows:

**Fusion method/melting method**

The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it get melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved. Such a technique was subsequently employed with some modification by Goldberg et al. and Chiou and Riegelman. The solidified masses were often found to require storage of one or more days in a desiccator at ambient temperatures for hardening and ease of powdering. Some systems, such as griseofulvin and citric acid, were found to harden more rapidly if kept at 370 C or higher temperatures.

This method has some limitations:
1. Many drugs can be degraded at such high temperature.
2. Incomplete miscibility between drug and carrier that may occur, because of the high viscosity of a polymeric carrier in the molten state. To avoid the melting method limitations, several modifications, like hot-stage extrusion, Meltrex TM or melt agglomeration were introduced to the original method.
Meltrex TM is a patented solid dispersion manufacturing process, also on the basis of the melting process. This technique includes the use of a special twin screw extruder and the presence of two independent hoppers in which the temperature can vary over a broad temperature range. In this process, residence time of drug reduces in the extruder, allowing a continuous mass flow and avoiding thermal stress to the drug and excipients. Additionally, it is possible that the application of this technique to protect drugs susceptible to oxidation and hydrolysis by complete elimination of oxygen and moisture from the mixture.

Another modification of the above given method, involves solid dispersion of drug and carrier like troglitazone- polyvinyl pyrrolidone K-30 have been prepared by closed melting point method. This method includes controlled mixing of water content to physical mixtures of troglitazone PVP K-30 by storing at various equilibrium relative humidity levels (adsorption method) or by adding water directly (charging method) and then mixer is heated. This method is reported to produce solid dispersion with 0% apparent crystallinity.

**Solvent evaporation method**
Various investigators have been prepared solid dispersion by using the solvent evaporation method. Tachibechi and Nakumara were the first to dissolve both the drug (β-carotene) and carrier PVP in a common solvent and then evaporate the solvent under vacuum to produce a solid dispersion. Mayesohn and Gibladi prepared solid dispersion by dissolving both griseofulvin and PVP in chloroform, and then evaporating the solvent. The release rate of griseofulvin form the solid dispersion was 5-11 times higher than that of micronized drug, depending on the drug/carrier ratio.

**Disadvantages solvent method**
- Difficulty in completely removing solvent.
- Possible adverse effect of remaining solvent on stability of drug.
- Difficulty of reproducing crystal form.
- Some other researchers have also used fusion method for preparing solid dispersion.

**Hot melt extrusion [26]**
Hot-melt extrusion (HME) technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms (Follonier et al., 1994; Zhang and McGinity, 1999, 2000; Ghebre-Sellassie and Martin, 2003). The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. This technique is same as the fusion method. The only difference is that in this method, intense mixing of the components is induced by the extruder. High shear forces results in to the high local temperature in the extruder and that can be problematic for the heat sensitive materials. There are some advantages over the conventional fusion method and those may be described as follows:
- This technique offers the potential to shape the heated the drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms.
- It also offers the possibility of continuous production, which makes it suitable for large scale production.
- It is a fast, simple, continuous, solvent free process requiring fewer processing steps than traditional tableting techniques.
- When used as a molding technique, there are no requirements for compressibility of the materials used in the formulation.
Alternative strategies: There are certain other approaches also those may be used for the preparation of solid dispersion as given as follows:

**Supercritical fluid technology (SCF):** SCF techniques can be adopted for the preparation of solvent free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Super critical fluid is the one where substances existing as a single fluid phase above their critical temperature and pressure. Methodology includes a very fine dispersion of hydrophobic drug in the hydrophilic carrier. Carbon dioxide is the most commonly used SCF because it is chemically inert, non toxic and non flammable.

**Co-precipitation method:** In this method, while during constant stirring, a non solvent is added drop wise to the drug and carrier solution and the drug and carrier are co-precipitated to get micro particles, and then this microparticle suspension is filtered and dried.

**Electrostatic spinning method:** This technology is used in polymer industry wherein it combines solid solution/dispersion technology with nanotechnology. In this process, a potential between 5 and 30 kV is applied on the liquid stream of a drug/polymer solution. And as when the electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibres of submicron diameter are formed. After evaporating the solvent, the formed fibres can be collected on a screen.

**Dropping method:** The dropping method was developed by Büllau and Ulrich (1977) to facilitate the crystallization of different chemicals. This method is a new procedure for producing round particles from melted solid dispersions. Methodology includes that the solid dispersion of a melted drug–carrier mixture is dropped onto a cooling plate, where it get solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that, when the melt is dropped onto the plate, it solidifies into a spherical shape. The dropping method does not use organic solvents and therefore has none of the problems associated with solvent evaporation.

**Marketed Study [21]**
- Gris–PEG, a griseofulvin-PEG fusion method solid dispersion was manufactured initially by Dorsey / Sandoz reached the market in the mid 1970s. Gris-PEG was developed as tablet product and this led to USP monograph for graseofulvin tablet. The solid dispersion form is referred to as ultramicrosize griseofulvin tablet USP and offers improved bioavailability and two-third reduced dosage compared to griseofulvin tablets USP.
- Cesamet, a nabilone-PVP solvent method solid dispersion manufactured by Eli Lilly and Co. has been marketed internationally since 1982. Eli Lilly discounted marketing Cesamet contains PVP and corn starch as in active ingredients and is presented capsule product.
- Solid dispersion formulation of Troglitazone (Rezulin) is marketed by Parke-Davis.
- Solid dispersion of Lopinavir and ritonavir in polyvinylpyrrolidone-vinyl acetate copolymer successfully enabled a reformulation of "Kaletra" (Abbott Laboratories, Abbot
Park, IL). In addition to reducing the dosage burden from six softgel capsule to four tablets. Tablets made with the need for refrigeration.

- “Sporanox” (Janssen Pharmaceutica, Titusville NJ) is solid dispersion of itraconazole in hypromellose that has been layered onto sugar spheres.

- The most recently approved product is non nucleoside reverse transcriptase inhibitor “Intelence” (Tibotec, Yardley, PA), an amorphous, spray dried solid dispersion of etravirine, hypromellose and microcrystalline cellulose.

References


