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SOLID DISPERSION TECHNIQUE FOR POORLY SOLUBLE DRUG

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- **ABSTRACT**

Formulation of solid dispersion in water-soluble carriers has been widely researched over the past four decades for solubility and related bioavailability enhancement. Despite 40 years of active research, there has not been much products in market based on this technique. The main reason for this being stability and scale up problems associated with this method, as reported by several authors. Strategies used for overcoming these problems and factors affecting formation of solid dispersion such as glass transition temperature and interaction of drug with polymer have been dealt conceptually in this review. The advent of surface-active carriers such as Gelucires, Poloxamers, and lipid -based carriers has given a new dimension for the successful development of solid dispersions by combating the problems associated with stability and also giving products with enhanced dissolution rate. Therefore, the article also discusses properties of such carriers that are being unraveled lately for formulation of solid dispersion. Characterization of solid dispersion to detect the change from crystalline to amorphous states and vice versa is an important tool for its formulation and determination of stability; thus, all the methods that are available for characterizations are discussed in this article with emphasis on the principle of the technique and its application.

- **KEYWORDS:** Poorly soluble drugs, Solid dispersion.

- **INTRODUCTION**[1,2,4,5]

Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Formulation development would lead to be failure if drug having poor aqueous solubility. The low dissolution rate and low solubility of drug substances in

water in aqueous G.I.T fluid frequently leads to inadequate bioavailability. The venture to improve the solubility and dissolution of hydrophobic drugs remain one of the trickiest tasks in drug development. Several methods have been introduced to triumph over this problem.

For enhancement of solubility and dissolution rate of poorly soluble drugs, abundant commercially viable methods are available such as liquisolid, in which drug in solution state or dissolved drug is adsorbed over insoluble carriers. To improve wettability and solubility of various lipophilic substances surfactants can also be used in formulations. Micronization of drug is not ideal because micronized product has the propensity of agglomeration, which leads to reduced effective surface area for dissolution. But solid dispersion is the mainly promising method to formulators because of its simplicity of preparation, ease of optimization, and reproducibility. The term 'solid dispersion' has been employed to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability.

The mechanism by which the solubility and dissolution rate of the drug is augmented includes: the particle size of the drug is abridged to submicron size or to the molecular size in the case where solid solution is achieved. The particle size reduction usually enhances the rate of dissolution; the changed from crystalline to amorphous form, the high energetic state which is very soluble; finally the wettability of the drug particle is enhanced by the dissolution carrier. Regardless of these promising advantages, the application of solid dispersion in pharmaceutical industry has certain boundaries With the recent dawn of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has increased sharply and the formulation of poorly soluble compounds for oral delivery currently presents one of the most frequent and utmost challenges to formulation scientists in the pharmaceutical industry.

Only small amounts of solid dispersion products are commercially exist. This is due to their poor physical characteristic for dosage form formulation. The solid dispersions prepared by employing water soluble carrier are soft and tacky mass which is hard to handle, particularly in the capsule-filling and tablet making development e.g, pulverization, sieving and mixing.

- **Noyes Whitney Equation**[3,4]

The rate of dissolution can be expressed by using Noyes whitney equation, which provides various parameters that can help improve the bioavailability of a poorly soluble drug.

$$dc/dt = AD (Cs-C)/ h$$

dc/dt- is the rate of dissolution

A- Surface area available for dissolution

D- Diffusion coefficient of the compound

Cs- solubility of the compound in the dissolution medium

C- Concentration of drug in the medium at time t

h- Thickness of diffusion boundary layer adjacent to the surface of dissolving compound

The main possibilities or improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the size of the particles present in the solid compound by optimizing the wetting phenomenon of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but not definitely the least, to enhance the apparent solubility of the drug molecules under physiologically relevant conditions. The absorption of drug from the gastrointestinal (GI) tract can be limited by several factors with the most important contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule.

While delivering an active agent orally, it is very much important that it must dissolve in gastric and/or intestinal fluids before it can reach systemic circulation through GI membrane permeability. Hence, a drug with poor aqueous solubility will exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will basically exhibit permeation rate limited absorption. Thus, two areas of pharmaceutical research that focus on improving the oral bioavailability of the active agents include enhancing solubility and dissolution rate of poorly water-soluble drugs and increasing the permeability of poorly permeable drugs.

- **Several Approaches For Enhancement Of Drug Dissolution/ Bioavailability Of Poorly Soluble Drugs**[2]

I. Physical modifications

- Particle size
- Micronization
- Nanosuspensions

- Modifications of the crystal habit
- Polymorphs
- Pseudopolymorphs (including solvates)
- Complexation/solubilization
- Utilization of surfactants
- Utilization of cyclodextrines
- Dispersion of Drug in a carrier
- Implication of Eutectic mixtures
- Solid dispersions (non-molecular)
- Solid solutions

II. Chemical modifications

- Soluble prodrug approach
- Salt formation

Bioavailability is defined as the rate at which the relative amount of an administered dose of a drug reaches to the systemic circulation from its site of administration. Various factors that influence the bioavaibility of the drug includes the gastric emptying rate, physiochemical properties of the drug, drug formulation type, enzymes induction/inhibition by other drugs/ foods, circadian differences, transporters, diseased state, health of the gastrointestinal tract etc. As the contents of GI tract are aqueous in nature, hence a drug with poor aqueous solubility possesses low saturation solubility which is correlated with a low dissolution rate, resulting a poor oral bioavailability. About 60% of drugs coming directly from synthetic origin have solubility below 0.1mg/ml.

- **Introduction Of Solid Dispersion**[4,6,7]

Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs. Sekiguchi and Obi were the first to describe on solid dispersions in 1961. Solid dispersion is one of the important strategies to tackle dissolution rate-limited oral absorption of poorly soluble compounds. Formulation of poorly soluble compounds as solid dispersions might lead to particle size reduction, improved wetting, reduced agglomeration, changeability in the physical state of the drug molecules and possibly a dispersion in the molecular level, according to the physical state of the solid dispersion. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a

hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drugs can be dispersed molecularly, either in amorphous particles (clusters) or in crystalline particles.

- **Definition**[8]

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate or sustained release of drug, altered solid state properties and improved stability.

- **Advantages of Solid Dispersion**[5,8,9]

a) ***Particles with reduced particle size:*** Molecular dispersions, as solid dispersions, represent the last stage of particle size reduction, and thus the drug possess a molecular dispersion in the dissolution medium after the dissolution of its carrier.

b) ***Particles with improved wettability:*** A strong contribution to the enrichment of drug solubility is related to the drug wetability improvement verified in solid dispersions. Carriers with surface activity, such as bile salts and cholic acid, when used, can potentially increase the wetability properties of drugs.

c) ***Particles with higher porosity:*** Particles with solid dispersions have been observed to have a higher degree of porosity. The increased porosity of solid dispersion particles also accelerates the drug release profile.

d) ***Drugs in amorphous state:*** Poorly water soluble crystalline drugs, in their amorphous state tend to have a higher solubility. However, the enhancement of drug release can usually be obtained using the drug moiety in its amorphous state, as no energy is required to break up the crystal lattice in the interim of dissolution process. In case of solid dispersions, drugs are conferred as supersaturated solutions after the system dissolves, and it is speculated that, if drugs precipitate, then it could be converted into metastable polymorphic form with a higher solubility than its most stable crystal form.

- **Disadvantages**[8,9]

✓ Carriers with High melting point cannot be used.

✓ Thermal degradation or instability may result at the melting point.

✓ Decomposition may take place, often dependent upon composition, fusion time and rate of cooling.

- ✓ Sublimation or Evaporation and polymeric transformation of the dispersion component may take place.
- ✓ Solidified melt may be tacky and unhandable.

- **Classification of Solid Dispersion**[10,11]

Solid dispersions are classified by various ways, on the basis of their solid state structure as well as on the basis of carrier used. It is relevant to classify various systems of solid dispersion as per as their fast release mechanisms are concerned. Riegelman and Chiou classified solid dispersions into the following six representative types: Simple eutectic mixtures, amorphous precipitations in a crystalline carrier, solid solutions, glass solutions and glass suspensions, compound or complex formation, and combinations of the previous five types. Given below is classification of solid dispersion on the basis of carrier used and solid structure in Figure 1 & 2 respectively.

→ **Classification of solid dispersion on the basis of carrier used**

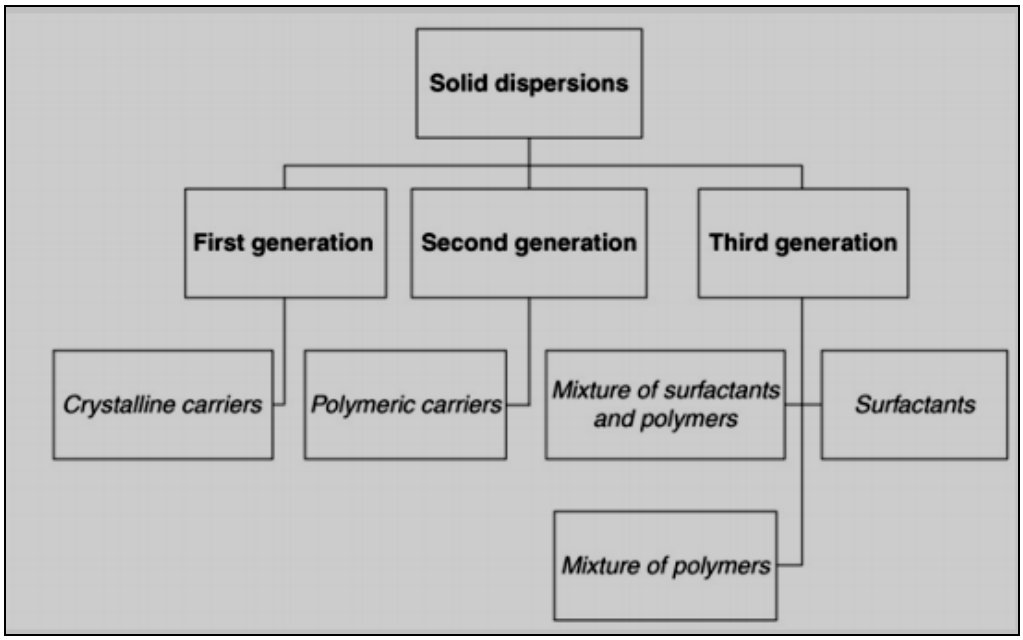

Figure 1: Classification of solid dispersion on the basis of carrier used.

A. First generation

The first generation solid dispersions can be developed by using crystalline carriers like urea and sugar, which were the first carriers to be imparted in solid dispersion. They are having the disadvantage of forming crystalline solid dispersion, which were thermodynamically more stable and cannot release the drug as quickly as amorphous ones.

B. Second generation

In second generation solid dispersions, amorphous carriers are used instead of crystalline carriers, which are usually polymers. These polymers include synthetic polymers such as poly vinyl pyrolidone (PVP), polyethylene glycols (PEG), ethyl cellulosepolymethacrylates, natural product based polymers such as hydroxylpropylmethyl-cellulose (HPMC) and hydroxypropyl cellulose or starch derivatives like cyclodextrins.

C. Third generation

Recently, it has been observed that the dissolution profile can be improved further, if the carrier has surface activity or self-emulsifying properties. Therefore, third generation solid dispersions were developed. The use of surfactant such as inutec SP1, inulin, compritol 888 ATO, gelucire 44/14 and poloxamer 407 as carriers were shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.

→ ***Classification of solid dispersion on the basis of solid structure***

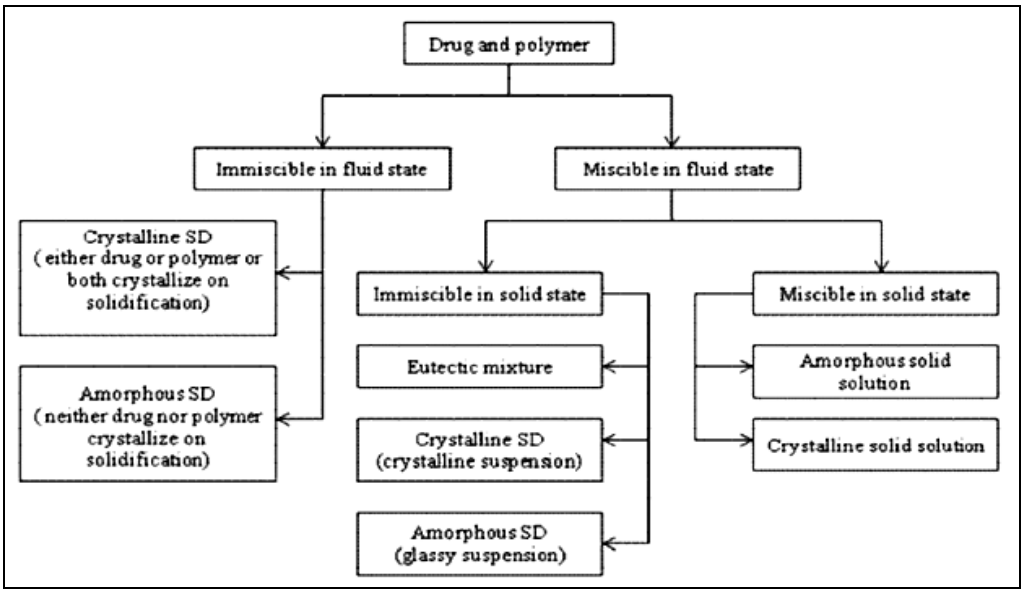

Figure 2: Classification of solid dispersion on the basis of solid structure.

A. Drug and polymer exhibiting immiscibility in fluid state

In case a drug and polymer are immiscible in their fluid state, it is expected that they would not exhibit miscibility on solidification of the fluid mixture. Hence such systems might be considered as similar to their corresponding physical mixtures and any short of enhancement in dissolution performance may be leading to modification in morphology of drug and/or polymer due to the physical transformation (i.e., solid to liquid state and back), enhanced surface area and/or intimate drug - polymer mixing.

B. Drug and polymer exhibiting miscibility in fluid state

If the polymer and drug are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, thus influencing the structure of solid dispersion.

C. Eutectic mixtures

Eutectic mixtures were first described as solid dispersions in 1961 by Sekiguchi & Obi. Eutectic mixtures are formed when the polymer and drug are miscible in their molten state, but on cooling, they crystallize just like two distinct components with negligible miscibility.

D. Crystalline solid dispersion

A crystalline solid dispersion is developed when the rate of drug crystallizes from drug-polymer miscible mixture is greater than that of the rate at which drug-polymer fluid mixture solidifies.

E. Amorphous solid dispersion

If the drug-polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then drug is kinetically trapped in its amorphous or a "solidified-liquid" state. Such types of dispersions have a high risk of potential for conversion to a less soluble and more stable crystalline form.

- **Solid Solution**[12]

Solid solution is defined as a solid dispersion which is miscible in its solid as well as fluid state. These solid solutions may be either of amorphous or crystalline type. In case of amorphous solid solutions, since the drug is molecularly dispersed in the carrier matrix, hence its effective surface area is predominantly higher and thus the dissolution rate of that drug is increased. Crystalline solid solution may results when a crystalline drug is trapped within a crystalline polymeric carrier.

As per as the miscibility of the two components is concerned, the solid solutions are either continuous or discontinuous type. In continuous solid solutions, the two components are miscible in the solid state in all proportions. The components that are miscible at extremes of composition but immiscible at intermediate composition are referred to as discontinuous solid solutions.

As per the criteria of molecular size of the two components are concerned, the solid solutions are classified as interstitial and substitutional. In the substitutional solid solution, the solute molecule substitutes the solvent molecule in the crystal lattice but, in case of interstitial solid solution, it is obtained when the solute (guest) molecule occupies the interstitial space in the solvent (host) lattice.

- **Preparation of Solid Dispersions**[12,13,14]

Various methods are used for preparation of solid dispersion system. These methods are depicted in figure 3.

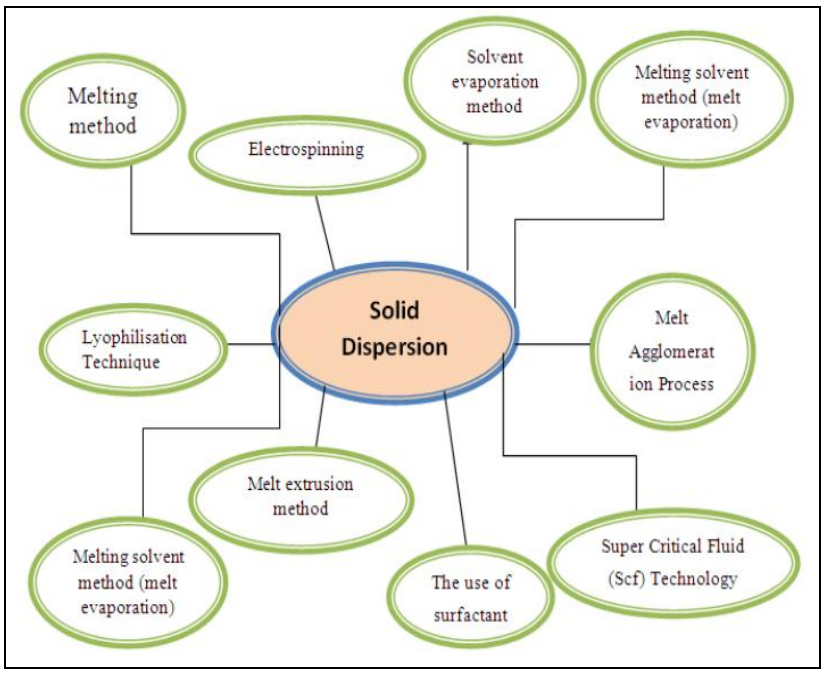

Figure 3: Methods of preparation of solid dispersions.

These methods are

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.

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.

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.

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 1min, 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 >355µ.

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 (PVPVA)], polyethylene oxide (PEO), Eudragit® (acrylates), Polyethylene glycol (PEG) and cellulose derivatives.

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.

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.

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.

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.

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 antisolvent, 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.

- **Characterization of Solid Dispersion**[15,16]

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion.

→ **Differential scanning Caloriemetry (DSC)**

Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC). In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

→ **X-ray diffraction (XRD)**

Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material.

→ **Infrared Spectroscopy (IR)**

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material.

→ **Water vapour sorption**

Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

→ **Hot stage and electron microscopy**

→ **Raman Spectroscopy**

→ **Dissolution testing**

In vitro dissolution studies are done for the find out dissolution behavior. The in-vitro dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through in vitro - in vivo correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed in-vivo dissolution study will be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately.

→ **Scanning Electron Microscope (SEM)**

→ **Methods for determination of residual solvents** (e.g. GC, Karl-Fischer, Loss on drying or nondestractive methods like NIR) Among these, thermal and spectral methods (i.e. DSC, XRD and IR) are of special interest.

→ **Solubility Studies**

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

→ **Temperature Modulated Differential Scanning Calorimetry (TMDSC):** Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC.

→ **Confocal Raman Spectroscopy**

Confocal Raman Spectroscopy is used to measure the homogeneity of the solid mixture. It is described that a standard deviation in drug content smaller than10% was indicative of homogeneous distribution. Because of the pixel size of 2 µm3, uncertainty remains about the presence of nano-sized amorphous drug particles.

- **SELECTION OF CARRIER**[17,18]

One of the most important steps in the formulation and development of solid dispersion for various applications is selection of carrier. The properties of carrier have a major influence on dissolution characteristics of the drug. A material should possess following characteristics to be suitable carrier for increasing dissolution:

a) Freely water-soluble with intrinsic rapid dissolution properties
b) Non-toxic nature and pharmacologically inertness
c) Thermal stability preferably with low melting point especially for melt method
d) Solubility in a variety of solvents and should pass through a vitreous state upon solvent evaporation for the solvent method
e) Ability to increase the aqueous solubility of the drug
f) Chemical compatibility and not forming a strongly bonded complex with drug.

- **POLYMERS USED IN SOLID DISPERSIONS**[16,17]

A variety of polymers is offered as carriers for formulation of solid dispersion. Some polymers used in solid dispersions are as follows:

A) Polyethylene Glycols (PEG)

The term polyethylene glycols refer to compounds that are obtained by reacting ethylene glycol with ethylene oxide. PEGs with molecular weight more than 300,000 are commonly termed as polyethylene oxides.

B) Polyvinyl Pyrrolidone (PVP)

PVPs have molecular weights ranging from 10,000 to 700,000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not suitable for preparation of solid dispersions prepared by melt method because it melts at a very high temperature above 275ºC, where it gets decomposed.

C) Polymers and Surface Active Agent Combinations

The addition of surfactants to dissolution medium lowers the interfacial tension between drug and dissolution medium and promotes the wetting of the drug thereby they enhance the solubility and dissolution of drug. Ternary dispersion systems have higher dissolution rates than binary dispersion systems.

D) Cyclodextrins

Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment of hydrophobic solute in hydrophilic cavity of CD. Advantages of CD include increasing the stability of the drug, release profile during gastrointestinal transit through modification of drug release site and time profile, decreasing local tissue irritation and masking unpleasant taste.

E) Phospholipids

Phospholipids are major structural components of cell membranes. Phosphotidylcholine was first isolated from egg yolk and brain. In phosphatidyl ethanolamine and phosphatidyl serine, the choline moiety is replaced by ethanolamine and serine respectively. Other phospholipids that occur in tissues include phosphotidyl ethanolamide, phosphotidyl serine and phosphotidyl glycerol. Naturally occuring lecithins contain both a saturated fatty acid and unsaturated fatty acids with some exceptions.

Table 1: Materials used as carrier for solid dispersion.

Sr. No.	Category	Examples
1	Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol, Mannitol
2	Acids	Citric acid, Succinic Acid
3	Polymeric materials	PVP, PEG, HPMC, HPC
4	Insoluble/ enteric polymer	Phthalate, Eudragits
5	Surfactants	Polyoxyethylene stearate, Renex, Poloxamers texafor, Deoxycholic acid, Tweens, Spans
6	Miscellaneous	Pentaerythritol, Pentaerythrityl tetra acetate,

- **Marketed Products**[18,19]

A list of several marketed products prepared using different solid dispersion techniques is given in table;

Product/Substance	Dispersion Polymer or Carrier	Technology used	Company
Gris-PEG® (Griseofulvin)	Polyethylene glycol	Melt process; exact process unknown	Novartis
Sproramax capsules (Itraconazole)	Hydroxypropylmethylcellulose (HPMC)	Spray layering	Janseen pharmaceutica
Cesamet®(Nabilone)	Povidone	process unknown	Lilly
Kaletra (lopinavir and ritonavir)	Polyvinylpyrrolidone (PVP)/polyvinyl acetate	Melt-extrusion	Abbott Laboratories
Torcetrapib[a]	HPMC acetate succinate	Spray drying	Pfizer
Ibuprofen	Various	Melt-extrusion	Soliqs
Isoptin SRE-240 (Verapamil)	Various	Melt-extrusion	Soliqs
Rezulin[b] (Troglitazone)	PVP	Melt-extrusion	Pfizer
LCP-Tacro (Tracrolimus)	HPMC	Melt-granulation	Life Cycle Pharma
Intelence (Etravirine)	HPMC	Spray drying	Tibotec
Certican (Everolimus)	HPMC	Melt or Spray drying	Novartis
Afeditab (Nifedipine)	Poloxamer or PVP	Melt/absorb on carrier	Élan Corp

- **Future Prospects**

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful developments of solid dispersion systems for preclinical, clinical and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points.

The preparation of dosage forms involves the dissolving of drug in melted carriers and the filling of the hot solutions into hard gelatin capsules because of the simplicity of manufacturing and scale up processes, the physico-chemical properties and, as a result, the bioavailability of solid dispersions are not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts of drug 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.

One major focus of future research will be the identification of new surfaceactive and self-emulsifying carriers for solid dispersion. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may the inadequate drug solubility in carrier, so a wider choice of carriers will increase the success of dosage form development.

Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention must be given to any physiological and pharmacological effects of carriers used. Many of the surfaceactive and self-emulsifying carriers are lipidic in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP-3 based drug metabolism and p-glycoprotein-mediated drug efflux will require careful consideration.

In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed toward the development of extended-release dosage forms. Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, an exemplified by the recent withdrawal of ritonavir capsules from the market, so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problems that might not be seen in other types of solid dosage forms. Predictive methods will be necessary for the investigation of any potential crystallization of drugs and its impact on dissolution and bioavailability, possible drug-carrier interactions must also be investigate.

- **CONCLUSION**

The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a solid dispersion method. The preparation method and the amount of the carrier also play a vital role in the enhancement of drug dissolution rate. With future development of this technology, solid dispersions will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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