International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 5(5): September-October 2015

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 12-06-2015; Revised: 19-09-2015; Accepted: 20-09-2015

SOLID DISPERSION: A PATHFINDER FOR SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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Keywords:

Solubility, Solid dispersion, Carrier, Bioavailability, Mechanism of drug release

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ABSTRACT

Over 40 % active pharmaceutical ingredients (API) in development pipelines poorly water soluble which limit formulation approaches, clinical application and marketability because of their low dissolution and bioavailability. Solid dispersion of poorly water soluble drug with water soluble carriers has reduced the incidence of the problem and enhanced dissolution .Solid dispersion is one of the most promising approaches for solubility enhancement. The term solid dispersion refers to a group of solid of sold product consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug .This article review recent advance in formulation ,preparation and characterization of solid dispersion.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration. [1] According to the Biopharmaceutics Classification System (BCS), A drug compound is poorly soluble if the highest dose strength is not soluble in 250 ml aqueous media over the pH ranges at 37^0C [3SD.]and Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Therefore lots of efforts have been made to increase dissolution of drug. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents, prodrug formation, particle size reduction,complexation , micelles , micro-emulsions, nanoemulsions , nanosuspensions , solid–lipid Nanoparticle. 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 drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. In Fig 1 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.[9]

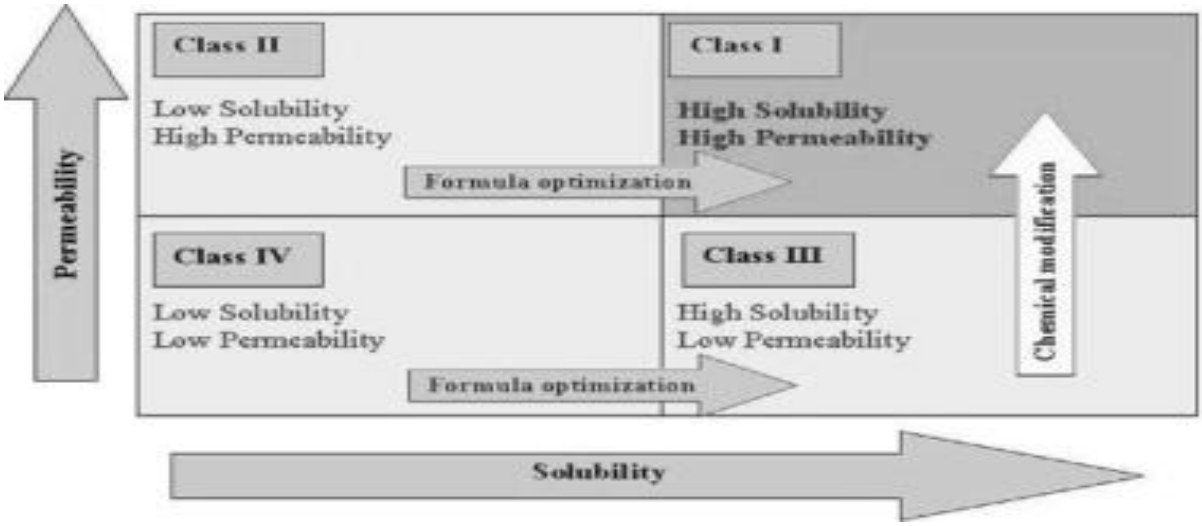

Figure 1 Bio pharmaceutics (BCS) classification

The classification of solid dispersions:

The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. They are described in Table 3. Moreover, certain combinations can be encountered, i.e in the same sample, some molecules are present in clusters while some are molecularly dispersed. Confusingly, in various studies the designation of solid dispersions is based on the method of preparation. However, since different preparation methods can result in the same subtypes or similar preparation methods can result in different subtypes, it can be argued that solid dispersions should preferably be designated according to their molecular arrangement. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions[43]. Therefore, it is essential to use terms that indicate the molecular arrangement in the solid dispersion. Knowledge about the molecular arrangement will enlarge comprehension of the properties and behaviour of solid dispersions. Furthermore, it will facilitate optimization of their properties required for a specific application. For example, the mechanism underpinning the dissolution of solid dispersions is poorly understood. Many case studies showed accelerated dissolution of hydrophobic compounds using solid dispersions but mechanisms are rarely discussed. The most important reason for that is the lacking knowledge about the mode of incorporation of the hydrophobic drug in the matrix, despite numerous efforts to clarify this. A question like, "is the drug present as a crystalline phase or as amorphous nano-particles or molecularly dispersed throughout the matrix" is rarely discussed. All three situations result in different drug concentrations at the dissolving interface[12]. Still it has not been fully elucidated how this affects dissolution behaviour of solid dispersions. Secondly, the physical and chemical stability of the matrix or the incorporated drug depends on the mode of incorporation. If drug molecules, for example, are present in amorphous nano-particles, crystallization requires only rotational rearrangement. On the other hand, for a dispersed drug, translational diffusion is necessary before crystallization can occur by rotational rearrangements. The physical state of the matrix is also important for the chemical stability of the drug: he crystallinity of the matrix influences the translational and rotational of the drug necessary for degradation reactions[8]. Finally, the influence of drug load and method of preparation on dissolution behaviour and stability of solid dispersions can only be understood and predicted when the relation between these characteristics and the mode of incorporation is known.[4]

SOLID DISPERSION		matrix *	drug **	Remarks	no. phases
I	Eutectics	C	C	the first type of solid dispersions prepared	2
II	amorphous precipitations in crystalline matrix	C	A	rarely encountered	2
III	solid solutions				
	Continuous solid solutions	C	M	miscible at all compositions, never prepared	1
	discontinuous solid solutions	C	M	partially miscible,2 phases even though drug is molecularly dispersed	2
	Substitutional solid solutions	C	M	molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinous: 2 phases even though drug is molecularly dispersed	1 or 2
	Interstitial solid solutions	C	M	drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinous. Example: Drug in helical interstitial spaces of PEG.	2
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
V	Glass suspension	A	A	particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
VI	glass solution	A	M	requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP	1

	Related and other designations				
	Complex formation	C/A	M	drug and matrix strongly interact and form complexes in aqueous environment. e.g. cyclodextrins or solid surfactants	1
	monotectics	C	C	same as eutectics but eutectic melting convergent with pure material, for completely non-interacting systems	2
	co- precipitates	?	?	prepared by addition of non-solvent to solution of drug and matrix	?
	co- evaporates	?	?	prepared by vacuum drying, spray drying, freeze drying and spray-freeze drying, many examples	?

*: 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

Mechanism of drug release from solid dispersions:

There are two main mechanisms of drug release from immediate release solid dispersions: drug-controlled release and carrier-controlled release. When solid dispersions are dispersed in water, the carriers often dissolve or absorb water rapidly due to their hydrophilic property and form concentrated carrier layer or gel layer in some cases. If the drug dissolves in this layer and the viscosity of this layer is high enough to prevent the diffusion of the drug through it, the rate limiting step will be the diffusion of the carrier into the bulk phase and this mechanism is carrier-controlled release. If the drug is insoluble or sparingly soluble in the concentrated layer, it can be released intact to contact with water and the dissolution profile will depend on the properties of drug particles (polymorphic state, particle size, drug solubility). In fact, these two mechanisms often occur simultaneously because the drug may be partly soluble or entrapped in the concentrated carrier layer. However, these mechanisms help explain the different release behaviours of solid dispersions and figure out the way to improve the dissolution profile of solid dispersions[21]. Numerous researches showed the improvement of drug dissolution profile when the ratio of carriers in solid dispersions was increased because the drug was dispersed better and the drug crystallinity decreased. In these solid dispersions the main release mechanism is drug-controlled release. In contrast, other researches demonstrated the decrease in drug dissolution rate when the ratio of carrier in solid dispersions was increased. This can be explained by the carrier-controlled mechanism in which the gel or concentrated carrier layer is formed and acts as a diffusion barrier to delay drug release. The release mechanism may also be affected by the ratio of drug–carrier in solid dispersions. Therefore, in order to improve the dissolution profile of solid dispersions, it is important to identify the mechanism release of solid dispersions rather than only focus on the polymorphic state of drugs because in carrier-controlled release solid dispersions, the carrier properties such as solubility, viscosity, gel forming ability and the ratio of drug–carrier are the key factors affecting the drug dissolution profile[19]. In CRSD, depending on the characteristic of polymers and the miscibility of the drug and carrier there are two main mechanisms by which the drug can be released from the system: diffusion and erosion. If the drugs and polymers are well dispersed in internal structure of solid dispersions, the diffusion of drugs through the matrix will be the main mechanism. If the drugs and carriers exist in separated particles, the solid dispersion erosion may become the main mechanism for drug release. In some solid dispersion, both of these mechanisms can control the drug release at the same time[27].

Advantages of solid dispersions:

Particles with Reduced Particle Size:

Molecular dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium. A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water soluble drug [8]

Particles with Improved Wettability:

The solubility enhancement of the drug is related to the drug wettability improvement verified in solid dispersion. Carrier with surface activity such as cholic acid and bile salts. When used can significantly increase the wettability property of drug.[13]

Particles with higher porosity:

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in amorphous state:

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility .The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.[66]

Disadvantages of solid dispersions:

The major disadvantages of SDs are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility. Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness.

Methods of preparation of solid dispersions

Various methods used for preparation of solid dispersion system. These methods are

1 Melting method

2 Solvent method

3 Melting solvent method (melt evaporation)

4 Melt extrusion methods

5 Supercritical anti solvent method

6 Melt agglomeration Process

7 The use of surfactant

8 Electrospinning

9 Fluid-bed coating

1 Melting 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 melted. 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[16]. 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[67]. 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[45].

2. Solvent method:

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. 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 [32] . However, some disadvantages are associated with this method such as

1) The higher cost of preparation.

2) The difficulty in completely removing liquid solvent.

3) The possible adverse effect of traces of the solvent on the chemical stability

4) The selection of a common volatile solvent.

5) The difficulty of reproducing crystal form.

6) In addition, a super saturation of the solute in the solid system cannot be attained except in a System showing highly viscous properties.

3. Melting solvent method (melt evaporation):

In the solvent evaporation method, solid dispersion is obtained after the evaporation of solvent from the solution containing a drug and carrier. The solvent method has solved main problems of the melting method relating to the decomposition of drugs and carriers at high temperature because in the solvent method, the solvent removal can be performed without heat such as freeze drying technique. Some polymers hardly used as carriers in the melting method due to their high melting point can be applied in the solvent method. An important prerequisite of this method is the sufficient solubility of the drug and carrier in a solvent or co- solvent. Finding a suitable non-toxic solvent is sometimes difficult because carriers are hydrophilic whereas drugs are hydrophobic. The solvents used in solvent method may include methanol, ethanol, ethyl acetate, methylene chloride, acetone, water...and mixtures thereof. Some surfactants such as Tween 80 and SLS can be utilized to increase the solubility of drugs and carriers in solvents. However, their incorporation has to be carefully considered, because a large excess may induce a significant change in the matrix structure. The disadvantage of this method is that the residual solvent remaining after evaporation process may cause toxicity and complete solvent removal is nearly impossible. In addition, residual solvent can also, like water, lower the Tg and act to plasticize the system, leading to phase separation due to the increased mobility of components. The use of solvent mixtures has been proposed as the way to minimize the problems relating to organic solvents. For example, Kumar used a dioxane–butanol–water mixture to prepare an amorphous solid dispersion of an opioid antagonist. Other disadvantages of the solvent method are its large environmental issues, the high cost of production due to the extra facilities required for solvent removal and protection against explosion as well as low scalability. For these reasons, hot melt extrusion is more favorable than solvent method to prepare solid dispersions if the stability and bioavailability enhancement of solid dispersions prepared by hot melt extrusion are ensured. Similar to the melting method, the solidification rate in solvent method can determine the

physical state of drugs in solid dispersions[3]. A fast solidification method is always preferred to guarantee the amorphous state of drugs. Therefore, there are many methods developed for fast solvent removal such as heating on a hot plate, vacuum drying, rotary evaporation, spray drying , freeze drying , spray freeze drying and ultra rapid freezing

4. Melt extrusion method:

The drug/carrier mix is typically processed with a 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 thermo labile to be processed [1]. 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 concentration of drug in the dispersions is always 40% (w/w).

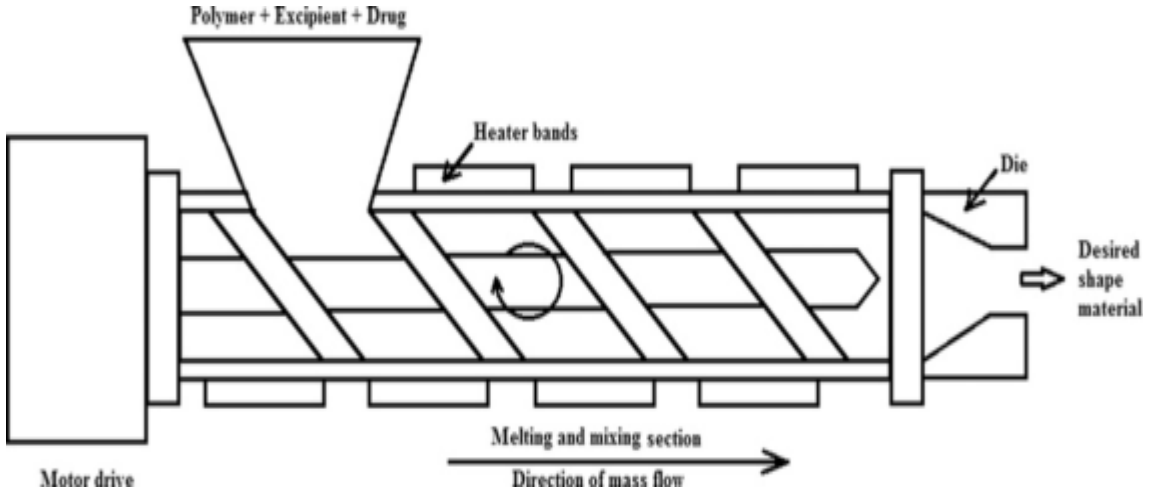

Figure 2 Schematic diagram of hot melt extrusion.

The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185C from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory cutting mill and sieve to exclude particles >355µm[1].

5. Supercritical anti solvent method:

In recent years, processing of pharmaceuticals with supercritical fluids has received increased attention. The supercritical fluid exists as a single fluid phase above its critical temperature

and critical pressure. Carbon dioxide is the most commonly used supercritical fluid. Depending on the method by which solution and supercritical fluid are introduced and mixed into each other, different terminology have been used by different researchers: (a) precipitations from supercritical solutions by rapid expansion of supercritical solution, (b) precipitation from saturated solution using supercritical fluid as an antisolvent, (c) precipitation from gas saturated solutions. Supercritical antisolvent related to various processes may be aerosol solvent extraction system (ASES), solution enhanced dispersion by supercritical fluids (SEDS), gas anti solvent (GAS), and supercritical antisolvent (SAS).[9] Schematic diagram of the supercritical antisolvent apparatus is shown in Fig. 4.

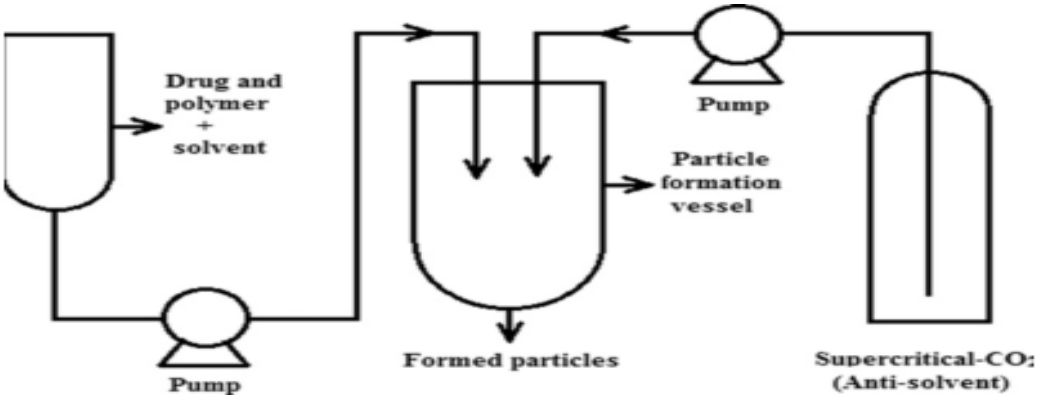

Figure 3 Schematic diagram of the supercritical antisolvent apparatus

In GAS or SAS process a mixture of drug and polymer is sprayed through an atomizer into a chamber filled with supercritical fluids. The expansion and extraction of organic solvent into the compressed gas result in lowering the solvent power of organic solvent for drug and polymer leading to precipitation Duarte et al. prepared acetazolamide composite microparticles by supercritical anti-solvent technique using Eudragit RS100 and RL100 as carriers for ophthalmic drug delivery. The composite particles in the size range of 8–40 lm were produced by semi-continuous process and batch process. Particles prepared by the batch process had a mean diameter larger than that produced by semi-continuous process. Composite particles containing Eudragit RS led to a slower release of drug than those containing Eudragit RL. Moreover, particles prepared by batch process exhibited faster release than those prepared by the semi-continuous process[25].

6 .Melt agglomeration method

In general, the amorphous solid dispersion prepared by melting method are soft, sticky and have poor flow properties and poor compressibility which hinder their applications in a large

pharmaceutical scale of tableting [43]. Melt agglomeration method, in which the carrier acts as a meltable binder, is a feasible method to solve these problems. Melt agglomeration is processed in high shear mixers or rotary processor with the mixture prepared by three ways: adding the molten carrier containing the drug to the heated excipients , adding the molten carrier to a heated mixture of the drug and excipients , or heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier.[33] The rotary processor may be preferable to the high shear mixer in melt agglomeration technique because the temperature can be more easily controlled and higher binder content can be incorporated in the agglomerates Seo et al. prepared the agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer.[53] This study showed significant increase in dissolution rate of diazepam and a higher dissolution rate was obtained with a lower drug concentration indicating a higher degree of molecular dispersion at the lower concentration.[31] It was concluded that the dissolution rate was affected mainly by the type of meltable binder since Gelucire 50/13 gave rise to faster dissolution rate compared to PEG 3000.

7 The use of surfactant:

The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobisity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency,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.[6]

8 Electrostatic spinning.

Electrostatic spinning (electrospinning) can be considered a combination of solid dispersion technology and nanotechnology. In this method, a drug–polymer solution is placed into a spinneret connected with a microsyringe pump and a high voltage between 5 and 30 kV is applied to the needle tip to induce a charge on the surface of the solution. A fixed electrical potential is also applied across a fixed distance between the spinneret and the collector . When electrical forces overcome the surface tension of the feeding solution at the air interface, polymer jets are ejected. After coming out, the charged jets go straight for somedistance, and then travel a spiral path because of the whipping instability. As the jet

accelerates through the electric field, the solvent evaporates rapidly to make fibers at micron or sub micron diameter which are collected on the screen or a spinning mandril. The collected fibers produce a non-woven fabric, which can be used in oral dosage forms by direct incorporation of the materials into a capsule or by further processing such as milling or grinding . In this process, the diameter and morphology of the filaments are affected by solution surface tension, the polymer solution dielectric constant, feeding rate, the electric field strength, tip-to-collector distance as well as some environmental parameters such as temperature, humidity and air velocity in the spinning chamber. The main advantage of this technique relates to the extremely high surface area per unit mass of fibers which facilitates the fast and efficient solvent evaporation leading to the formation of amorphous dispersions. Therefore, the dissolution of the API incorporated in these fibers is improved significantly by two mechanisms: nanosizing and amorphization .Yu et al. prepared PVP based solid dispersions of acetaminophen using electrostatic spinning and compared with other methods. The results showed that electrospun nanofiberbased solid dispersions had significantly faster dissolution profile compared to other casting-film solid dispersions prepared by vacuum drying, freeze drying, and heat-drying.[1]

9 Fluid bed coating

In this method, the drug and carrier are firstly dissolved in a solvent. This solution mixture is sprayed through a nozzle onto the surface of nonpareil pellet in a fluid-bed coater. The solvent is removed by drying airflow and the co-precipitate simultaneously deposited on the surface of nonpareil pellets. The advantage of this method is that solid dispersion granules or pellets can be ready for tableting or encapsulating into capsules without further handling. As showed in the researches of Sun et al, solid dispersions prepared by fluid-bed coating demonstrated the bioavailability improvement of fenofibrate and silymarin in vivo.[1]

Characterization of physicochemical properties

The dissolution enhancement of poorly water-soluble drugs in solid dispersions can be proven by the standard dissolution methods. Other properties of solid dispersions such as the physical states of drugs, the drug–carrier interaction and the physical and chemical stability of drugs should also be evaluated. Consequently,many instrumental and analytical techniques are applied to measure these properties. The crystalline state of drugs and the degree of crystallinity are importantly characterized. The amount of drugs existing in amorphous state can be calculated indirectly from the extent of crystallinity in the sample. The crystalline state of drugs is commonly characterized by the following techniques: thermoanalytical techniques

such as Differential Scanning Calorimetry (DSC) and Modulated Differential Scanning Calorimetry (MDSC); powder X-ray diffraction (PXRD); Confocal Raman Spectroscopy. Other instrumental techniques such as Fourier Transformed Infra- red spectroscopy (FTIR), solid state nuclear magnetic resonance, Thermal Gravimetry Analysis (TGA) are used to investigate the chemical stability and molecular interaction of the drug and carrier. Microscopy techniques such as optical microscopy, transmission electron microscopy (TEM), scanning electron microscopy (SEM) and atomic force microscopy (AFM) are also used to qualitatively characterize the crystalline states of drug, the molecular miscibility, phase separation and surface morphology of solid dispersions.

1. Differential Scanning Calorimetry (DSC) and Modulated Differential Scanning Calorimetry (MDSC)

The basic principle of thermal analytical approaches is the dynamic changes in the solid-state properties of material initiated by the heating or cooling process. DSC, the most commonly used thermal technique for solid dispersion characterization, provides accurate information about melting point, glass transition temperature as well as the energy changes associated with the phase transitions including crystallization and fusion process. The lack of a drug melting peak in the DSC thermogram of a solid dispersion indicates that the drug exists in an amorphous form. In DSC, the glass transition endotherm, crystallization exotherm and fusion endotherm can also be quantified and used to calculate the degree of crystallinity[1]. For instance, Urbanetz used DSC to evaluate the remaining amorphous content of a drug in solid dispersions during storage conditions. However, the degree of crystallinity which is under 2% may not be detected by DSC. DSC parameters, such as endotherm ((ΔH_{tr}, J/g), was also used to predict the bioavailability of solid dispersion products by Berndl et al. . It was concluded that the solid dispersions of itraconazole improved bioavailability as ($\Delta H tr < 0.35$ J/g and the lower endotherm of solid dispersions obtained when the higher energy inputted during melt extrusion process led to bioavailability improvement. Modulated DSC is an advanced thermal technique that can deconvolute the different thermal events obtained from DSC. In MDSC, a sinusoidal wave modulation is superimposed on top of the conventional linear temperature ramp allowing the separation of total heat flow in DSC into reversing and non-reversing thermal transition. Thermal events such as enthalpic relaxation, evaporation, crystallization, thermal decomposition and some other melting events are distributed in the non-reversing heat flow while the reversing heat flow includes other melting events and glass transition. The application of this MDSC technique in solid dispersion characterization has

become very popular due to its advantages such as the improvement of both sensitivity and resolution, analysis of complex overlapping transitions, direct measurement of the heat capacity and detection of weak glass transitions compared to standard DSC. As described by Guinot and Leveiller, MDSC method was successfully used to detect and quantify low levels of amorphous phase in crystalline drug through measurements of the heat capacity jump associated with the amorphous phase glass transition. Ghosh et al. tried to develop a stable amorphous solid dispersion of a poorly water-soluble and highly thermal sensitive compound by hot melt extrusion. Preliminary MDSC studies showed that propylene glycol was the most suitable plasticizer which could provide single phase. solid dispersion of the API with various polymers and also facilitate low processing temperatures. The molecular miscibility, recrystallization and phase separation of solid dispersions after preparation and under accelerated stability conditions were characterized by MDSC. In this study, a single Tg of solid dispersions showed molecular miscibility and a new Tg detected by MDSC indicated phase separation. The solid dispersion system was physically stable if no re-crystallization peaks were observed.

2. Powder X-ray diffraction (PXRD)

PXRD is the most widely used method to identify and characterize the crystalline state of drugs in solid dispersions. This method can detect material with long-range order as well as expose sharp diffraction peaks that indicate crystalline compound with characteristic fingerprint region. Thanks to the specificity of the fingerprint, the drug crystallinity can be separately identified from the carrier crystallinity and thus can differentiate the amorphous state and crystalline state of drugs in solid dispersions. However, the crystallinities under 5–10% fraction may not be detected by PXRD.

3. Fourier Transformed Infrared spectroscopy (FTIR)

FTIR is a common technique used to investigate the intermolecular interaction and drug–carrier compatibility because it can detect the physical and chemical reaction between drug and carrier[35]. Hydrogen bonding between drugs and carriers which is very important to explain the physical state and the stability of drugs in solid dispersions can also be identified by FTIR. Miyazaki et al. studied the crystallization rates of nitrendipine (NTR) enantiomers in the presence of HPMC, HPMCP and PVP. FTIR results indicated that PVP interacted with NTR through hydrogen bonding at the NH moiety of NTR, and almost the same degrees of shift in wavenumber for NH stretching suggested a similar strength of hydrogen bonding interaction for enantiomers: (-)NTR and (+)NTR. Therefore, similar degree of physical

stability between (-)NTR and (+)NTR was observed in PVP based solid dispersions whereas the overall crystallization rate and the nucleation rate of (+)-NTR were lower than those of (-)NTR in HPMC or HPMCP based solid dispersions because of stereoselective interaction between enantiomers and these carriers.[50] The hydrogen bonding between PVP and NTR also explained for the lower growth rate of NTR crystal in PVP based solid dispersions compared to HPMC and HPMCP based solid dispersions.

4. Thermal Gravimetry Analysis (TGA)

TGA is a method of thermal analysis that measures the weight as a function of time and temperature, thereby providing information about the stability of a material and the compatibility of different materials in a solid dispersion mixture. This method can provide useful information about the stability of drugs and carriers as well as the chemical and physical processes in solid dispersions to decide the preparation method and the processing parameters for solid dispersion preparation. Other common applications in the pharmaceutical sciences include the determination of moisture and solvent content as well as decomposition, vaporization or sublimation temperatures [70]. However, this technique is not effective for materials that do not exhibit a weight change during degradation and some processes which do not involve the loss of mass. Similar to DSC method, TGA results are changeable and depend on the conditions of sample and experimental process which is difficult to compare the work of one researcher to another. Frizon et al. used TGA method to check the thermal stability of loratadine in the temperature range of the preparation process and the biocompatibility of loratadine and PVP in solid dispersions. The results showed that loratadine was stable up to 203 ^{0}C at which it started losing mass. The thermo analytical curves of solid dispersions and their components were not significant dif-ferent, which suggested that chemical interactions accelerating drug or polymer degradation did not occur. Physicochemical characterization of solid dispersions is essential to evaluate the pharmaceutical applicability of solid dispersions and thoroughly understand the pharmaceutical mechanisms of drug dissolution enhancement and physicochemical stability. Therefore, an ongoing development of new and advanced characterization techniques in solid dispersion area is very necessary[35].

CONCLUSION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. So to improve the aqueous solubility of the drugs, many techniques have been adopted since decades and solid dispersion is one of those

techniques. Many techniques that can be used for the formulation of solid dispersion have already been discussed in the article. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution .The focus of this review article on advantages, disadvantages and the method of preparation, and characterization of the solid dispersion.

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