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Review Article

Solid Dispersion: A Review

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ABSTRACT
Solid dispersion is one of the techniques for improving the dissolution rate by increasing the solubility. Many scientists have been attracted towards this technique as a way of improving bioavailability of drugs mainly those belonging to Biopharmaceutic Classification System class II and IV. Aim of writing this review article is to give detail insight into the solid dispersion, their types based on the molecular arrangement, various methods of their preparation along with characterization. This article discusses various methods of preparation of solid dispersions that mainly depend upon the types of surface active carrier and selection of which plays an important role in the successful preparation of solid dispersion. The present review proves the importance of solid dispersion in the area of drug delivery and will definitely help research scientists struggling hard to increase the oral bioavailability of various poorly soluble drugs.

Keywords: Bioavailability, Biopharmaceutic Classification System, Dissolution, Drug delivery, Polymeric carriers, Solid dispersion, Solubility.

INTRODUCTION

The therapeutic effect of drug depends on the drug concentration at the site of action. The absorption of drug into the systemic circulation is prerequisite to reach the site of action.[1] As only dissolved drug can pass the gastrointestinal (G.I.) membrane, dissolution is one of the factors that determine the bioavailability of orally administered drugs.[2] In general, it can be stated that the rate of absorption, the onset and the extent of clinical effect is determined by dissolution of drug and the subsequent transport through the intestinal membrane and passage to the liver. These two aspects form the basis of the biopharmaceutical classification system (BCS).[3] According to BCS four different types of drug absorption regimes (Table I) are distinguished.

Table 1: Biopharmaceutical Classification System

Class	Solubility in aqueous Environment	Permeability (GI membrane)
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

The progress in the treatment of diseases has been evident with an increase in the development of new drugs. However, recent report suggests that 46% of the total NDAs filed with USFDA were BCS class IV, while only 9% were BCS class I drugs, revealing that a majority of approved new drugs were water insoluble and unfortunately, many of these potential drugs are abandoned in the early stages of development due to solubility concerns.[4] As the rate limiting step for absorption and thus bioavailability of class II drugs is solubility i.e. dissolution in an aqueous environment, efforts are made towards increasing solubility/dissolution rate in order to enhance their bioavailability and thus performance. However, the solubility/dissolution in an aqueous environment and permeation over the membrane are said to be the rate limiting steps for bioavailability of class IV drugs and in order to increase the bioavailability, the dissolutions and the permeability both have to be increased. Practically increasing dissolution rate is more effective than increasing the permeability of drug as the amount of dissolved drug at absorption site varies over six orders of magnitude (0.1 μg/ml to 100 μg/ml) while permeability varies over only a 50 fold range. Therefore, to improve the performance of class II and IV drugs, one has to concentrate over the methods that will enhance the dissolution of these drugs rather than permeability over membrane. There are various techniques which have been noted to improve the

dissolution rate of poorly water soluble drugs like micronization,[5] formation of inclusion complexes with cyclodextrin,[6] formation of amorphous drug,[7] formation of solid dispersions with polymeric carrier and chemical modification[8] etc. A review of the literature reveals that several hundred citations and reviews describes the effects of complexation on dissolution and bioavailability of drugs such as Spironolactone,[9] Tolbutamide,[10] Ketoprofen,[11] Danazol[12] etc.

Although particle size reduction and salt formation are the commonly used techniques to increase the dissolution rate of drug, however, there are few practical limitations associated with these techniques and hence the newer formulation approaches are being explored to enhance the bioavailability of poorly water soluble drugs. Preparation of solid dispersion using polymeric carriers is one of the approaches that have shown the ability to enhance the bioavailability of such poorly water soluble drugs. In the following text an attempt has been made to discuss about the solid dispersions techniques in detail.

Solid Dispersion

Historically, the term "solid dispersion" was defined as a dispersion of drug in a solid matrix where the matrix was either a small molecule or polymer.[13,14] The dispersed state is being included in various forms such as eutectic mixtures, crystalline/glass solutions and amorphous/crystalline suspensions. Taking into account its currently most-used form, a solid dispersion can even more narrowly defined as dispersion of drug in an amorphous polymer matrix where the drug is preferably in the molecularly dispersed state.

Advantages of Solid Dispersions

1. The rapid dissolution rates that result in an increase in the rate and extent of absorption of drug and a reduction in pre-systemic metabolism. This later advantage may occur due to saturation of the enzyme responsible for biotransformation of drug as in the case of 17-β-estradiol,[15] morphine–tristearin dispersion[16] that lead to lower doses of the drug.
2. Transformation of liquid form of drug into solid form. e.g. Clofibrate and benzoyl benzoate can be incorporated into polyethylene glycol (PEG) 6000 to form a solid.[17]
3. Avoidance of polymorphic changes and there by bioavailability problems. e.g. nabilone and polyvinylpyrrolidone (PVP) dispersion.[18]
4. Practically viable method to enhance bioavailability of poorly water soluble drug that overcome the limitation of previous approaches such as salt formation, solubilization by co-solvent and particle size reduction.[19] e.g. Law et al. explored solid dispersion systems for improved oral bioavailability and efficacy of the oral treatment of HIV.[20]
5. No need to have the drug in micronized state.[21]
6. Desired modified release characteristics for drug can be obtained by incorporating polymer with controlled release properties. e.g. Hasegawa et al.[22] and Sugimoto et al. [23] developed a solid dispersion formulation of nifedipine with PVP and enteric polymers and evaluated formulations in dogs and humans. The formulation showed rapid absorption of drug along with sustained blood level in dogs and humans.

In spite of the above advantages, very few products have been marketed since the development of this technology 4 decades ago.[24] This technology has some drawbacks that impede the commercialization of solid dispersions and these impediments are:

1. Instability: Several systems have shown changes in crystallinity, e.g. with aging, a decrease in dissolution rate and crystallization of ritonavir from the supersaturated solution in a solid dispersion system responsible for withdrawal of the ritonavir capsule (Norvir, Abbott) from the market.[25]
2. Moisture and temperature have more deteriorating effect on solid dispersions than on the physical mixtures.[26]
3. Some solid dispersion may not lend themselves to easy handling because of tackiness.[26]
4. Laborious and expensive method of preparation as costly solvents and instruments may be required for preparation of solid dispersions by some techniques.
5. Difficulty in reproducibility of physicochemical characteristics of drug such as particle size, shape and surface area.
6. Difficulty in incorporating into the formulation of dosage forms.
7. Poor scale-up for the purposes of manufacturing.[24]

Mechanism of increased dissolution rate from solid dispersion

The enhancement in the dissolution rate as a result of solid dispersion formulation relative to pure drug varies from as high as 400 fold to less than two fold. More than one factor is responsible for enhancements of dissolution rate of drug from solid dispersions and these factors are:

Formation of Fine Colloidal Particles

When solid dispersions exposed to the dissolution media, the carrier which is/are present in the solid dispersions dissolve first and the drug is released as a fine colloidal particles resulting in enhanced surface area and overall enhanced dissolution rate and thus bioavailability. In addition to this, in solid dispersions a portion of drug dissolves immediately to saturate the dissolution media/GI fluid and excess drug precipitates as fine colloidal particles or oily globules of submicron size.[24]

Increased Amorphous Nature of the Drug

It was observed from powder X-ray diffraction (PXRD) and differential scanning calorimetric (DSC) studies of solid dispersions that decreased crystallinity and increased amorphous nature of drug can also be responsible for an enhanced dissolution rate. Jain et al.[27] prepared the solid dispersion of terbinafine hydrochloride and performed solubility studies and PXRD study on the same and observed the reduction in the crystallinity and increased in amorphous characteristics of drug that has attributed to increase in the solubility of terbinafine hydrochloride.

Solubilization Effect

The carrier material, as it dissolves, may have solubilization effect on the drug e.g. acetaminophen and chlorpropamide in urea, as well as numerous other drugs.[28]

Wettability and Dispersibility

The carrier material may also have enhancing effect on wettability and dispersibility of the drug in dissolution media that retards any agglomeration or aggregation of particles that can slow the dissolution process. Okonogis et al. prepared binary solid dispersion of water insoluble ofloxacin with PEG of different molecular weights in the ratio of 5:5 and ternary solid dispersion system containing ofloxacin/PEG4000/polysorbate 80 in 5:5:1 w/w/w. The PXRD and DSC studies indicated that crystalline ofloxacin existed in the solid dispersions with high drug loading. The results indicated a remarkable improvement in the dissolution of the drug from the ternary solid dispersion systems when compared with the binary solid dispersion systems. The improvement in dissolution was attributed to polysorbate 80, which improved wettability and solubilized the non–molecularly dispersed or crystalline fraction of ofloxacin.[29]

Types of Solid Dispersions

As we have seen earlier, the term solid dispersion refers to a group of solid products consisting of at least two types of 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. Therefore, based on their molecular arrangement six different types of solid dispersions can be distinguished namely Eutectic system,[13] Amorphous precipitation,[30,31] Solid solutions,[32-34] Glass suspension made up of polymer matrix in amorphous form and drug in the crystalline form and Glass suspension having both polymer matrix and drug in amorphous form[35] and Glass solution.[36] Solid solutions are further subdivided into four types namely Continuous Solid solution, Discontinuous Solid solution, Substitutional Solid solution, Interstitial Solid solution. The detail description regarding the types of solid dispersion is given in the work of Dhirendra et al.[37]

Preparation of Solid Dispersion

Various preparation methods for solid dispersions have been reported in the literature. These methods deal with the challenge of mixing a polymer matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, demixing (partially or complete) and formation of different phases was observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. It was already recognized in one of the first studies on solid dispersions that the extent of phase separation can be minimized by a rapid cooling.[30,32] Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation can be prevented by maintaining the driving force for phase separation low, e.g. by keeping the mixture at an elevated temperature and thereby maintaining sufficient miscibility as long as possible.

The two basic procedures used to prepare solid dispersions are the fusion and co-solvent techniques. Recently, application of supercritical fluid process has also been explored to form pharmaceutical solid dispersions. The techniques commonly used to prepare the solid dispersions are first four whereas rests of the techniques have also been explored to lesser extent by the researchers.

Melting or Fusion Method

This method was first reported by Sekiguchi and Obi.[14] A physical mixture of an active pharmaceutical ingredient and a water soluble carrier is heated until melted. This melt was then solidified rapidly in an ice bath under vigorous stirring, pulverizing and then sieving. Rapid

congealing is desirable because it results in supersaturation of the drug as a result of entrapment of solute molecules in the solvent matrix by instantaneous solidification. The solidification process can be achieved on stainless steel plates attached to a cooling system to favor the rapid heat loss. Spray congealing from a modified spray drier onto a cold metal surface has also been used. Products obtained were in pellet form and without the necessity of a grinding step that may alter crystalline modification.

The fusion method sometimes referred to as the melt method, which is correct only when the starting materials are crystalline and hence term fusion method is generally preferred. The first solid dispersion for pharmaceutical application was prepared by the fusion method.[14] The dispersion consisted of sulfathiazole and urea as a matrix which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. PEG is mostly used to prepare solid dispersions with the fusion method as many drugs incorporated as separate molecule entraps in the helical structure of a crystalline PEG.

Yu¨ ksel et al.[38] evaluated a solid dispersion of piroxicam in a carrier system composed of Gelucire 44/14 and Labrasol. The dispersion was produced by a melt method in which piroxicam was stirred into the molten carrier system and subsequently the molten dispersion was filled into hard gelatin capsules. This formulation was comparatively evaluated against bulk piroxicam and a commercially available tablet containing piroxicam-β cyclodextrin complexes for in vitro drug release and in vivo absorption. Dissolution tests were conducted in various media and observed that the bulk piroxicam showed pH-dependant and incomplete dissolution, the commercial tablet showed substantial improvement in the dissolution properties of piroxicam; however, some pH-dependence was found with a reduction in release rate at pH 4.5 while the solid dispersion formulation provided rapid dissolution of piroxicam (85% in 30 min) irrespective of pH. The in vivo performance of these three piroxicam formulations was evaluated in healthy human volunteers and it was observed that the solid dispersion formulation provided the greatest maximum concentration (2.64 mg/mL) in the shortest time-to-peak (82.5 min), followed by the commercial tablet (2.44 mg/mL, 120 min) and the bulk drug (0.999 mg/mL, 144 min). These results indicated that the solid dispersion providing greater acceleration of absorption than the commercial tablet and bulk drug.

Melt method of preparation of solid dispersion is simple and economical as it does not require addition of solvents. However, there are various drawbacks associated with this method. Firstly, the method may not be suitable if the drug or the carrier is unstable at the fusion temperature or evaporates at high temperatures. Succinic acid, for example, used as a carrier for griseofulvin, is quite volatile and partially decomposes by dehydration near its melting point. These problems can be avoided by melting the material in a sealed container under vacuum or under an inert gas, such as nitrogen. By proper selection of carrier system and composition, the melting point of a binary system can be much lower than the melting point of either of the components. Secondly, this method may lead to the tacky and intractable nature of the resulting solidified melt and irregular crystallization owing to the presence of a miscibility gap on the phase diagram for a given drug–carrier system. Thirdly, the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. Two liquid phases or a suspension can be observed in the heated mixture when the drug and the matrix are incompatible[39] and this result in an inhomogeneous solid dispersion. This can be prevented by using surfactants.[40,41] Lastly, a problem can arise during cooling when the drug-matrix miscibility changes and phase separation can occur. Indeed, it was observed that crystalline drug was obtained when the mixture was slowly cooled whereas fast cooling yields an amorphous solid dispersion.

Solvent Evaporation Method

Tachibana and Nakamura first used this method to prepare a solid dispersion of β-carotene in PVP using chloroform as a co-solvent[42]. The solvent is usually removed by evaporation under reduced pressure at varying temperatures. The choice of solvent and its removal rate are critical to the quality of the dispersion. Some examples of solid dispersions prepared by this method include sulfathiazole–PVP[36], reserpine-deoxycholic acid[43] and griseofulvin–PVP[44]. The major advantage of the solvent method for the preparation of solid dispersion is that thermal decomposition of drugs and carriers associated with the fusion method can be avoided. The disadvantages of this method include the higher cost of preparation, the use of large quantities of the organic solvents and difficulty in its complete removal, the possible adverse effect of residual solvent, the problems in selection of a common volatile solvent, the difficulty of reproducing crystal forms and the inability to attain a super-saturation of the solute in the solid system unless the system goes through

a highly viscous phase. The solid dispersion can also be prepared using combinations of suitable solvent system.

The pharmaceutical engineer faces various challenges in the solvent method. The first 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,[45] preferably drug and matrix material are dissolved in one common solvent. Various strategies have been applied to dissolve the lipophilic drug and hydrophilic matrix material together in one solvent. Drug in very low concentrations is used with matrix material to dissolve it in water,[46] but this requires evaporation of large amounts of solvent thus making the process expensive and impractical. Solubilizers like cyclodextrin or surfactants like Tween80® increases the aqueous solubility of the drug substantially. However, the amount of solubilizers or surfactants in the final product is often eminent. This results in solid dispersions that, to a significant extent, consist of solubilizers or surfactants materials that significantly change the physical properties of the matrix (e.g. decrease in Tg). 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. Chloroform[47] or dichloromethane[40] have been used to dissolve both drug and PVP simultaneously. However these solvents belong to ICH class-I, meaning the most toxic solvents. The use of these solvents is therefore unacceptable and impractical as the amount of residual solvent present in the solid dispersion after drying has to be below the detection limits. The last strategy for the dissolution of both drug and matrix is the use of solvent mixtures. Water and ethanol[48] or dichloromethane and ethanol[49] have been used for this purpose. However, dissolution of drug and matrix in these mixtures is not always possible in the required concentration or ratio. 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 temperature speeds up the process and reduces the time available for phase separation.[50] On the other hand the molecular mobility of drug and matrix remains high at high temperatures favoring phase separation (e.g. crystallization). Vacuum drying is often used to dry the solutions.[51] Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. The formed solid dispersion is often stored in a vacuum desiccator to remove the residual solvent. Vacuum drying at an elevated temperature bears the risk of phase separation as the mobility of drug and matrix decreases slowly.

Spray drying is another drying technique. Here, the solution is dispersed as fine particles in the hot air and due to the large specific surface area offered by the droplets, the solvent rapidly evaporates. The solid dispersion is formed within seconds, which may be fast enough to prevent the phase separation. Moreover, the size of particles in the developed solid dispersions prepared may be customized by changing the droplet size to meet the requirements for further processing or application (e.g. free flowing particles or particles for inhalation). Spray drying usually yields drug in the amorphous state,[52] however, the drug may be (partially) crystallized sometime during processing.[53] Ambike et al.[54] applied this spray drying technique for the preparation of solid dispersions of amorphous simvastatin. The amorphous simvastatin solid dispersion was produced by spray drying of an organic solution of the drug and PVP along with aerosil 200 in various proportions and compared hypolipidemic activity of the 1:2:2 simvastatin:PVP:aerosil 200 solid dispersion with bulk simvastatin in healthy wistar rats that were administered excess coconut oil to promote hypercholesterolemia. From the results obtained through the study, Ambike et al. concluded that the solid dispersion formulation of simvastatin with PVP and aerosil 200 prepared by spray drying technique have better cholesterol lowering action than bulk simvastatin.

An alternative to these drying techniques is the freeze drying. Although this method of drying is reported in the literature as a promising and suitable to incorporate drug substances in stabilizing matrices.[55] However, this technique is poorly exploited for the preparation of solid dispersions and obvious reasons might be the low freezing temperature of most organic solvents and sublimation during freeze drying is only possible when the solvent stays frozen.[56,57] In addition, when the formation of a glass is envisaged, the sample temperature should be kept below the T_g of the maximally freeze concentrated fraction. Therefore, low sample temperatures are required so that process can be slowed down. Betageri and Makarla used a temperature of -75 ^{0}C to dry a solution with cyclohexanol.[47]

To obtain a lyophillization process of acceptable duration, the solvent should have high melting temperature and a high vapor pressure. Although, Dimethylsulphoxide (DMSO) has a high melting temperature, it has very low vapor pressure and therefore DMSO is not suitable solvent for freeze drying. A suitable solvent that meet both the requirements is 2-methyl-2-

propanol or tertiary butanol (TBA). The application of TBA in lyophilization is discussed by Teagarden and Baker.[58] An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. The most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. However, this method was found to be less efficient than co-solvent evaporation method in increasing the bioavailability. Sekikawa et al. compared cosolvent-evaporation method with freeze-drying method for preparation of solid dispersion of dicumarol in PVP and β-cyclodextrin.[59] The performance of formulated solid dispersions from both methods was evaluated using rabbit as a model and it was observed that the average AUC values (0-48h) of solid dispersion prepared by cosolvent-evaporation method was 3.31times and that of by freeze-drying method was 1.54 times that of dicumarol crystal powder (used as control). The corresponding numbers for β-cyclodextrin dispersions were 2.18 and 1.72.

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 result in even faster vitrification, thereby decreasing the risk for phase separation.[60,61] Moreover, spray freeze drying offers the potential to customize the size of the particles to make them suitable for further processing or applications like pulmonary [62] or nasal administration.[63]

In an electrostatic spinning process, a drug-matrix solution is pumped through an orifice and then subjected to an electrical field to form fibers with a diameter of micro- or nano-scale. This process is restricted to a limited amount of matrices because only a few high molecular weight materials are fiber forming materials. The fiber diameter can be adjusted by surface tension, electrical field and dielectric constant. After rapid evaporation of the solvent, the fibers can be directly used or milled.[64]

Evaporative precipitation into aqueous solutions (EPAS) was used to coat a colloidal suspension of carbamazepine with block-copolymers as stabilizing surfactants. A solution of drug in dichloromethane was sprayed in an aqueous solution containing polymeric surfactants as stabilizers. The obtained colloidal suspension was spray dried, freeze dried or spray-freeze dried to obtain solid dispersions.

Hot Melt Extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. As compared to melting in a vessel, the product stability and dissolution are similar,[65] but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts or oral dosage forms.[30] Solubility parameters needs to be investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder are a problem for heat sensitive materials.[51,65] However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding. Solubility and the dissolution rates of 17 β-estardiol hemihydrate was improved using PEG 6000, PVP or a vinylpyrrolidone/vinyl acetate-copolymer and Sucroester WE15 or Gelucire 44/14 employing this process.[66] Highly enhanced dissolution rate from extruded powder containing 10% 17 β-estardiol hemihydrates, 50% PVP and 40% Gelucire 44/14 was preserved when processed into tablets and met the United States Pharmacopeia (USP) XXIII requirements. Hulsmann et al. prepared solid dispersion of ibuprofen by melt-extrusion technique and compared with the ibuprofen lysinate in healthy volunteers. The solid dispersion prepared by this technique showed bioequivalency with the relevant parameters like area under the curve (AUC) and maximum concentration (C_{max}). Also the t_{max} as a measure for onset proved to be equivalent with 0.5 hours for test and reference.[67]

Supercritical Fluid Methods

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent.[68,69] When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique is known as rapid expansion of supercritical solution (RESS) and it does not require the use of organic solvents. CO_2 used in this method is considered environment friendly and hence this technique is referred to as 'solvent free'. However, the application of this technique is limited due to very low solubility (<0.01 %w/w) of most

pharmaceutical compounds in CO_2 and it further decreases with increasing polarity.[70] Therefore scaling up of this process to kilogram-scale is impractical. All other supercritical techniques are precipitation methods. Although generally labeled as solvent-free, all these supercritical fluid methods use organic solvents to dissolve drug and matrix and exploit the low solubility of pharmaceutical compounds in CO_2. In fact, these techniques represent alternative methods to remove solvents from a solution containing typically a drug and a polymer. Although, Moneghini et.al.[71] reported their method as solvent-free, but they dissolved PEG and carbamazepine in acetone. They used a technique that is called the gas-anti-solvent technique (GAS) or precipitation from gas saturated solutions (PGSS). In this technique, the solution is brought into contact with compressed CO_2 and the conditions are chosen so that CO_2 is completely miscible with the solution under supercritical conditions and the drug and matrix will precipitate upon expansion of the solution. When the volume of the solution expands, the solvent strength (i.e. the ability to dissolve the drug) decreases resulting in precipitation of matrix and drug. Since this technique is often applied with PEG as matrix, it often results in formation of a solid dispersion with a crystalline matrix.[72]

The second type of precipitation technique involves the spraying of a solution containing drug and matrix through a nozzle into a vessel that contains a liquid or supercritical anti-solvent. The supercritical anti-solvent rapidly penetrates into the droplets in which drug and matrix become supersaturated, crystallize and form particles. The general term for this process is precipitation with compressed anti-solvent (PCA). However, as with the other solvent techniques described in the previous section, the critical step in the precipitation techniques might be the dissolution of drug and matrix in one common solvent. The use of water is limited as the water solubility and/or miscibility with compressed CO_2 is limited. Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both the drug and the matrix.[68,70,72]

Kneading Technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.[4]

Co-precipitation method

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.[73]

Co-grinding method

Physical mixture of drug and carrier is mixed for some time operating a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill where steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Chlordiazepoxide and mannitol solid dispersion was prepared by this method.[74]

Gel entrapment technique

Hydroxyl propyl methyl cellulose (HPMC) is dissolved in an organic solvent to form a clear and transparent gel. Then drug is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under the vacuum. Solid dispersions are reduced in size by mortar and sieved.[75]

Spray-Drying Method

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer.[76]

Lyophilization Technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative method to solvent evaporation. 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.[47]

Electrospinning Method

The electrospinning technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology. In this procedure, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces prevail over the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are produced. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandrel.[77] This technique has tremendous potential for the preparation of nanofibers and controlling the release of biomedicine, as it is simplest and the

cheapest this technique can be utilized for the preparation of solid dispersions in future.[78]

Dropping solution method

The dropping method developed to facilitate the crystallization of different chemicals. It is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods. For laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvents and therefore has none of the problems associated with solvent evaporation.[4]

Melt Agglomeration Process

This technique has been used to prepare solid dispersion where the binder acts as a carrier. Solid dispersion(s) are prepared either by heating the binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug and molten binder on the heated excipient by using a high shear mixer.[79] A rotary processor has been shown to be alternative equipment for melt agglomeration because of easier control of the temperature and because higher binder content can be incorporated in the agglomerates.[80]

Characterization of Solid Dispersion

Detection of Crystallinity in Solid Dispersions

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Many attempts have been made to investigate the molecular arrangement in solid dispersions. Lot of efforts has been put in discriminating amorphous and crystalline material and many techniques are available that can detect the amount of crystalline material in the dispersion. The amount of amorphous material is never measured directly but is mostly derived from the amount of crystalline material in the sample.[81] It should be noted that through the assessment of crystallinity as method to determine the amount of amorphous drug, it will not be able to reveal whether the drug is present as amorphous drug particles or as molecularly dispersed molecules. Currently, the following techniques are available to detect the (degree of) crystallinity:

1. **Powder X-ray diffraction** (PXRD) can be used to qualitatively detect materials with long range order. Sharper diffraction peaks indicate more crystalline material. Recently developed X-ray equipment is semi-quantitative.

2. **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 Transform Infrared (FTIR) Spectroscopy was used to accurately detect crystallinity ranging from 1 to 99% in pure material. However, in solid dispersions only qualitative detection was possible.[82-85]

3. **Water vapor sorption technique** can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different.[86] This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples. In some studies, amorphous materials were plasticized by water sorption and crystallized during the experiment. However, crystallization can be accompanied by expel of water depending on the degree of hydration of crystalline material. In this case, the loss of water is used to calculate the amount of amorphous material. However, water vapor sorption in a binary mixture, e.g. solid dispersions, can be much more complicated than in pure materials. Firstly because water vapor sorption is not always proportional to the composition of a intimately mixed binary system and secondly matrix or drug crystallization during water vapor sorption is not often complete within the experimental time scale due to sterical hindrance and may proceeds to an unknown extent.

4. **Isothermal Microcalorimetry** measures the crystallization energy of amorphous material that is heated above its Tg.[87] However; this technique suffers from few limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes and thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

5. **Dissolution calorimetry** measures the energy of dissolution which is dependent on the crystallinity of the sample. Usually, dissolution of crystalline material is endothermic; whereas dissolution of amorphous material is exothermic.[88] The dissolution energies of the two components in both crystalline and amorphous state should be determined in separate experiments in order to use this technique quantitatively. However, drug-matrix interactions will also contribute to the dissolution energy of the solid dispersion.

6. **Macroscopic techniques** that measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and dynamic mechanical analysis (DMA) determine the modulus of elasticity and viscosity. However these techniques require the knowledge about the additivity of these properties in intimately mixed binary solids. The mode of incorporation of drug can also sometimes correlated with the extent of supersaturation during dissolution experiments of solid dispersions. It is unmistakable that the mode of largely incorporation of drug determines the dissolution behavior. The knowledge about dissolution behavior is too poor to draw any conclusions from dissolution experiments as it can't be excluded that crystallization of the drug occurs during dissolution.

7. A frequently used technique to detect the amount of crystalline material is differential scanning calorimetry (DSC).[89] 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 like glass to rubber transition, (re)crystallization, melting or degradation occur can be detected. Furthermore, the melting and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material. Possibly, the re-crystallization energy can be used to calculate the amount of amorphous material, provided that all amorphous material is transformed to the crystalline state. If during DSC-measurements, amorphous material crystallizes, information is obtained on the crystallization kinetics and on the physical stability of the amorphous sample. To quantify the amount of crystalline material, measurements should be completed before crystallization of amorphous material has started. In some cases, this can be established applying high scanning rates. Clearly, many techniques can discriminate between the crystalline and amorphous state for pure materials. However, in a mixture of two components like in a solid dispersion, it is always necessary to know the interaction between the individual component and the effect thereof on the physical property that is being quantified and from which the crystallinity is to be derived.

Detection of Molecular Structure in Amorphous Solid Dispersions

The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix. The stability and dissolution behavior could be different for solid dispersions that do not contain any crystalline drug particles. However, not only the knowledge on the physical state (crystalline or amorphous) is important, the distribution of the drug as amorphous or crystalline particles or as separate drug molecules is relevant to the properties of the solid dispersion too. Nevertheless, only very few studies focus on the discrimination between amorphous incorporated particles versus molecular distribution or homogeneous mixtures. However, not only the knowledge on the physical state (crystalline or amorphous) is important; the distribution of the drug as amorphous or crystalline particles or as separate drug molecules is relevant to the properties of the solid dispersion too. Nevertheless, only very few studies focuses on the discrimination between amorphous incorporated particles versus molecular distribution or homogeneous mixtures. Confocal raman spectroscopy was used to measure the homogeneity of the solid mixture of ibuprofen in PVP.[90] Researchers suggested that a standard deviation smaller than 10% in drug content was indicative of homogeneous distribution. However due to the pixel size of 2 μm^3, uncertainty still remained as the presence of nano-sized amorphous drug particles may go undetected.

FTIR spectroscopy can be used for the measurement of the extent of interactions between drug and the matrix. The interactions are indicative for the mode of incorporation of the drug as separately dispersed drug molecules will have more drug-matrix interactions than when the drug is present in amorphous clusters or other multi-molecule arrangements.[91,92] 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. In case of amorphous matrices, TMDSC has been used to discriminate between solid dispersions. Furthermore, the value of the glass transition 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[93] and therefore this technique can be used to assess the amount of molecularly dispersed drug[49] from which the fraction of drug that is dispersed as separate molecules can be calculated.[94] Moreover, the fraction of the drug present in amorphous state can be assessed.

Surface Active Carrier for Preparation Of Solid Dispersion

In addition to their use as an excipient for improving the physical and chemical characteristics of the formulation, the surface active carrier may be included to improve the bioperformance of the product by altering the thermodynamic activity, solubility, diffusion, disintegration and dissolution rate of the drug. Furthermore, the surface active carriers can exert direct effect on biological membranes thus altering drug transport across the membranes95. The surface active carriers and self emulsifying carriers for solid dispersions of poorly water soluble drugs have been of great interest in recent years. The dissolution characteristics of the dispersed drug in the solid dispersions are mainly influenced by the properties of the carrier while preparing the solid dispersions. The carriers should be chosen on the basis of the following criteria's:

1. Carrier should be freely water soluble with intrinsic rapid dissolution properties.
2. Carrier should be nontoxic and pharmacologically inert.
3. When using melting method, carrier should be stable with low as well as high melting point or when using solvent evaporation method should be stable with solvent evaporation temperature.
4. Should be soluble in variety of solvents.
5. Preferably it should be able to increase the solubility of drugs.
6. Should be chemically compatible with the drugs.
7. Should have high glass transition point to improve the stability.

Self emulsifying agent increases the dissolution of drug by preventing the formation of any water insoluble surface layer, although the liberated drug remains undissolved in the dissolution medium. When its concentration exceeds its saturation solubility, it will disperse or emulsify into a finely divided state because of surface activity of the dissolved vehicle which will facilitate its dissolution in G.I. fluid as the high surface area will be made available.[96]

Gelucire® 44/14 (Gattefosse corp. Gen ennevilliers France), a mixture of glyceryl and PEG 1500 esters of long chain fatty acids, has been commonly used in solid dispersions for the bioavailability enhancement of drugs.[97,98] It is official in European pharmacopoeia as a lauryls macrogolglycerides.[24] The suffix 44 and 14 in the name refers to its melting point and hydrophilic-lipophilic balance (HLB) value respectively.[99]

Chen et al. improved the dissolution and bioavailability of ABT-963, a poorly water soluble compound, by preparing its solid dispersion using pluronic F68 as a carrier using evaporation and hot plate method. The results of their study proved that the solid dispersion is a promising approach for increasing oral bioavailability.[100]

Gurusamy et al. formulated and investigated physical mixture of meloxicam with skimmed milk and solid dispersion prepared using rotary vacuum evaporation technique. Enhancement of aqueous solubility of meloxicam was observed with solid dispersion of the drug with skimmed milk due to amino acids and surface active agents present in the milk. The solid dispersion of the drug indicated a significant improvement in the dissolution of the drug as compared to the physical mixture and the pure drug. DSC, PXRD and scanning electron microscopic (SEM) analysis revealed the formation of solid dispersion of the drug with skimmed milk.[101]

Kumar et al. developed solid dispersion of terbinafine hydrochloride with PVP K-30 and suggested that dissolution rate of terbinafine hydrochloride increased due to solubilization, improved wetting and reduced crystallinity of drug in PVP K-30 rich microenvironment formed at the surface of drug crystals.[27]

Chowdary and Srinivas formulated ibuprofen suspensions employing its solid dispersion in hydroxylpropyl methyl cellulose (HPMC), PVP, PEG and dextrin and then evaluated all the formulations for particle size, physical stability and dissolution rate. They observed that solid dispersions of ibuprofen exhibited good suspendability along with higher dissolution rate as compared to formulation of suspension of ibuprofen alone and its commercialized product. Suspension formulated with solid dispersion in dextrin gave highest improvement in dissolution rate and efficiency. Excellent linear relationships were observed between particle size and dissolution rate and efficiency. Smaller particles gave higher dissolution rate and efficiency values.[102]

Madhusudhan et al. prepared the solid dispersion of sulphamethoxazole using mannitol as a carrier in various proportions, converted them into tables, evaluated and compared with some of the sulphamethoxazole-trimethoprime conventional tablets available commercially and suggested that tablets formulated by both wet granulation and direct compression methods containing solid dispersion of sulphamethoxazole–mannitol in the proportion of 1:2 prepared by melting and melt solvent method exhibited highest dissolution rate compared with some of the sulphamethoxazole–trimethoprime conventional tablets available commercially.[103]

Chaulang et al. converted furosemide into solid dispersion with cross-povidone in 1:1 (w/w) and 1:2 (w/w) and using solvent water and ethanol in 1:1 ratio. FTIR spectroscopy, DSC, and PXRD were performed and exhibited change in the crystal structure towards amorphous one of furosemide. These solid dispersion were also evaluated for dissolution rate and compared with commercially available tablet and they observed that the solid dispersion of furosemide with crosspovidone in 1:2 ratio have high dissolution rate by more than 5 fold.[104]

Shashikanth et al. prepared complexes of nimesulide by solvent evaporation method and solid dispersions of ibuprofen using fusion, solvent evaporation and fusion-solvent method. Solubility profiles of the drug from the solid dispersions and complexes of nimesulide were studied in buffered pH 6.6, whereas the solubility of drug-excipients dispersions of ibuprofen were evaluated in 0.1 N sodium hydroxide media. Solid dispersions of nimesulide with PEG-6000 enhanced the solubility of nimesulide by more than 1000% whereas solid dispersions of ibuprofen in sorbitol showed maximum enhancement of solubility (up to 75%). Dispersions in combined carriers: PVP K-30-microcrystalline cellulose (MCC) and PVP K-30-PEG6000 also markedly increased the solubility of ibuprofen.[105]

Summers and Enever produced the solid dispersion containing 1.32 % w/w primidone by fusing the drug with citric acid and rapidly cooling the melt and observed that solubility of primidone increased in the presence of citric acid and the increase in the solubility was greater than that of pure or physical mixture.[106]

Chen et al. developed the solid dispersion of docetaxel with poloxamer 188 and recommended that the solubility and dissolution of docetaxel from solid dispersion were markedly improved in comparison to pure docetaxel and its physical mixtures. The results of X-ray diffraction, DSC and environmental scanning electron microscope indicated that the physical-chemical interaction such as an association between the functional groups of docetaxel and poloxamer 188 might occur in molecular level and there was not any crystalline of docetaxel in solid dispersion at ratio of 10:90 (docetaxel to poloxamer 188) or in the increase of solubility and dissolution of docetaxel from the solid dispersion finally they suggested that solid dispersion using poloxamer 188 as carrier provides a promising way to increase the solubility and dissolution rate of poorly soluble drugs.[107]

Solid dispersion systems for improved oral bioavailability of tacrolimus by solvent evaporation method using mixed solvent system have recently been explored by Yamashita et al. The solubility of tacrolimus in water is 1–2 mg/mL and thus has shown low oral bioavailability. These researchers evaluated solid dispersion systems of tacrolimus with PEG 6000, PVP and HPMC in order to identify the optimum carrier. Dissolution testing was conducted in pH 1.2 medium with tacrolimus in excess of the saturation solubility to determine which carrier polymer would yield the greatest extent of super saturation. The results of this dissolution testing revealed that although each solid dispersion formulation showed equivalent peak super saturation concentrations that were 25-times that of saturation (50 mg/mL), the HPMC formulation was the only solid dispersion that was able to maintain these elevated concentrations for 24 h. This result demonstrated that HPMC can effectively prevent the precipitation of supersaturated tacrolimus which presumably would provide enhanced in vivo absorption and thus the tacrolimus-HPMC formulation was selected for oral bioavailability evaluation in beagle dogs. This study clearly indicated that the tacrolimus-HPMC solid dispersion formulation exhibited C_{max} and AUC values that were ten-fold higher than the crystalline powder. By the use of scanning electron microscopy, DSC and XRD it was determined that tacrolimus was present in the HPMC carrier in an amorphous state. Therefore, this solid dispersion formulation of tacrolimus has substantial potential for improving immunosuppressive drug treatment and thereby decreasing the frequency of transplantation rejection.[108]

Table II shows some other examples of drugs that have been converted into the solid dispersion along with the surface active carriers used for them.

Table 2: Surface active carriers for preparing solid dispersions

Surface active carriers	Drug	Researchers
PEG 6000, PEG 8000 PEG 2000, Laurel F127, β-Cyclodextrin.	Meloxicam.	Inamdarn et al. [109]
PEG 4000, PEG 5000, Mannitol, Urea, Sorbitol, Dextrose, Sucrose in 1:1	Ibuprofen	Ali & Sharma[110]
PEG 6000	Sulphamethoxazole & trimethoprime	Jain & Parikh.[111]
PVP & PEG	Glipizide	Himasankar et al.[112]
PEG 6000 & Poloxamer, Urea	Albendazole & mebendazole	Kalaiselvan et al.[113]
PEG 6000, HPMC 2910 E5	Itraconazole.	Janssens et al.[114]
PVP, PEG, PVP, Vinyl acetate.	Celecoxib.	Devi et al.[115]
PVP, Mannitol	Diclofenac. sodium.	Manjunatha et al.[116]
Pluronic F68 & gelucire 50/13	Nifedipine .	Vippagunta et al.[41]
Polysorbate 80, PVP K30.	Oleanolic acid	Longxiao et al.[117]

CONCLUSION

To improve the solubility and thus bioavailability of drugs belonging to BCS class II and IV, solid dispersion systems have been found to be most promising and effective tool in the field of drug delivery systems and thus improving the properties of such poorly water soluble drugs. In recent years, a number of researches have been carried out on solid dispersion technology, but their commercial applications have been found very limited due to various drawbacks behind different techniques. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. Moreover, various new, optimized technologies are also coming out along with various novel polymeric carriers or matrix materials through researches which are recently going on in academics.

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