Review Article

A basic insight into the stability and manufacturing aspects of solid dispersions

Abstract

The development of a bioavailable dosage form is the most challenging task for the researchers. In the arena of advanced drug delivery systems, the solid dispersion techniques seem to be a promising system for the development of an optimized, bioavailable formulation of Class 2 drugs. The methods of formulation of solid dispersion have been summarized. This article is an effort to define a solid dispersion and its classification. The prospective of the stability of solid dispersion has also been discussed. Moreover, the major techniques that have been used so far such as the fusion/melting method, solvent evaporation method, hot melt extrusion method, supercritical fluid methods, have also been detailed.

Key words:
Fusion method, hot melt extrusion method, solid dispersion, solvent evaporation method, stability of solid dispersion, supercritical fluid methods

Introduction

One of the most important problems faced by the drug formulators all over the world is the poor solubility of drug candidates. Most of the work currently going on in the drug formulation technology field is mainly concentrated on increasing the solubility characteristics of the drug synthesized. Development of an optimized, bioavailable formulation of a particular drug is a Herculean task. 40% of the drugs newly synthesized by the chemists belong to the category of poorly soluble drugs.[1,2] Development of bioavailable dosage form of these drugs is the most important challenge faced by the formulators. The oral route of administration is the most convenient and preferred method of drug delivery. At least 90% of all drugs used to produce systemic effects are administered by oral route. Of drugs that are administered orally, solid dosage forms represent the preferred class of product. After oral administration, factors like fraction of drug reaching the systemic circulation determine the bioavailability of the drug. In solid dispersion, a portion of drug dissolves immediately to saturate the gastrointestinal (GI) tract fluid and excess drug precipitates as fine colloidal particles or oily globules of submicron size.[3] A drug can be orally delivered only if it has good dissolution profile in GI fluids before it can pass through the membrane of GI tract to reach systemic circulation. According to Biopharmaceutical Classification System (BCS), drugs are classified into four types given in Table 1.[4,5]

Class 1 drugs dissolve rapidly in an aqueous environment and are rapidly transported over the absorbing membrane. From the point of view of a formulator, these types of drugs are perfect candidates and new strategies are not to be

Table 1: Biopharmaceutical classification system of drugs[4,5]

Class	Aqueous dissolution	Intestinal membrane permeability
I	Fast	Fast
II	Slow	Fast
III	Fast	Slow
IV	Slow	Slow

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devised for them. For Class 2 drugs, dissolution becomes the rate-limiting phenomenon as they have good permeability characteristics. The *in vivo* absorption can be affected by several physiological factors, like the volume and pH of the intestinal juices, the presence of bile salts, food, enzymes and bacteria, motility of the gut, and the viscosity in the gut lumen. Class 3 drugs have permeation as the rate-limiting factor. The strategy for this class of drugs depends on the transport mechanism over the permeation membrane. For the Class 4 drugs, both dissolution and permeation are limiting and it is the most difficult task for a formulator to device a bioavailable dosage form of such a drug. Solid dispersion technology is mainly focused on improving the dissolution and absorption characteristics of Class 2 drugs with poor aqueous solubility. A pharmaceutical literature survey related to solid dispersions revealed that the dissolution behavior of a number of poorly water-soluble drugs have been altered with the help of solid dispersion techniques. The oral bioavailability of Class 2 drugs can be increased.

Definition of Solid Dispersions

- A dispersion of one or more ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting solvent method.[6,7]
- A product formed by conversion of a fluid drug carrier combination to the solid state.
- Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug.

Classification of Solid Dispersions

As the term solid dispersion technique signifies, a hydrophobic drug is molecularly dispersed in the polymers in its amorphous or crystalline state. Based on the molecular arrangement, six types of solid dispersions are identified [Table 2].[7-9]

Discussion on stability of solid dispersions

The dissolution characteristics and chemical integrity of a solid dispersion must remain unaltered during its shelf life period. For accomplishing optimum stability in a solid dispersion, the molecular mobility should be as low as possible. Mostly, solid dispersions are amorphous in nature and therefore most of them prove to be thermodynamically unstable. Nucleation and crystallization occur in solid dispersions containing crystalline particles. The better side of a crystalline matrix is that diffusion will be very slow and so degradation. Literature shows that such solid dispersions show poor dissolution characteristics on storage. The three important steps which finally results in the instability of a solid dispersion are diffusion, nucleation, and crystallization.[8,10,11] A, B, C, and D in Figure 1, respectively represent molecularly dispersed drug, amorphous drug particles, partially crystalline particles, and crystalline drug particles.

Table 2: Classification of solid dispersions[7-9]

Solid dispersions	Matrix*	Drug**	No. of phases	Remarks
I				
Eutectics	C	C	2	1st solid dispersion
II				
Amorphous precipitations in crystalline matrix	C	A	2	Rarely encountered
III				
Solid solutions				
Continuous solid solutions	C	M	1	Never prepared
Discontinuous solid solutions	C	M	2	Partially miscible, drug is molecularly dispersed
Substitutional solid solutions	C	M	1 or 2	Molecular diameter of drug is $\leq$15% of polymer
Interstitial solid solutions	C	M	2	Molecular diameter of drug $\leq$ 59% of polymer. Limited miscibility and discontinuous
IV				
Glass suspension	A	C	2	Particle size of dispersed phase depends upon cooling/evaporation rate
V				
Glass suspension	A	A	2	Particle size of dispersed phase depends upon cooling/evaporation rate. Mostly encountered
VI				
Glass solution	A	M	1	Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation

*A: matrix in the amorphous state; C: matrix in crystalline state; **A: drug dispersed as amorphous clusters in the matrix; C: drug dispersed as crystalline particles in the matrix

Factors affecting the stability of solid dispersions

The physical state, molecular mobility, antiplasticization, drug-polymer ratio, molecular weight of the polymer, and drug–matrix interactions are the major factors that may affect the stability of solid dispersions.[11]

Physical state of solid dispersion

The crystalline state and the amorphous state are the two most important states of materials with respect to solid dispersions.[11,12] The crystalline state is a thermodynamically stable form because the particles have less mobility and they have lesser energy. Amorphous materials are thermodynamically unstable and have a natural tendency to change to the crystalline state.[13] The two important physical states that can be identified in amorphous materials are glassy and rubbery state and their characteristics are compared in Table 3.[11]

Molecular mobility in dispersion

Molecular mobility is one of the most important properties which determine the stability of a solid dispersion. It is related to macromolecular properties like viscosity, diffusion coefficient, and enthalpy Molecular mobility is quantified in terms of relaxation time (τ).[11,12,14]

Relaxation time

It is defined as the time required by a molecule or chain segment to diffuse across the matrix through a distance of one molecule or chain segment. Relaxation time varies with temperature. Typical relaxation times at glass transition temperature (T_g) are 100–200 seconds.

Glass transition temperature

It is defined as the temperature above which a material changes to a glass like consistency and share the properties of glass.[15]

In general, the glassy pharmaceutical solids should be expected to experience significant molecular mobility at temperatures up to 50°C below their glass transition temperature.[15]

Relaxation time at storage conditions indicates the shelf life period of a formulation. The extend of relaxation is mathematically represented with the help of Kohlrausch-Wiliams-Watts (Equation 1) here:

$$\varphi(t) = \exp[-(t/\tau^{\beta}] \quad 0<\beta<1 \qquad \text{(Equation1)}$$

$\varphi(t)$ =fraction of non relaxed material at time t

β = relaxation time distribution factor

Application of Kohlrausch-Wiliams-Watts equation[11]

1. It represents parameters that are used to classify solid dispersions into different glasses
2. It correlates temperature and relaxation time
3. The prediction of shelf life using relaxation time and relaxation time distribution factor can be performed
4. It also can be used to predict the viscosity changes in solid dispersions to some extent.

Literature reports the applicability of time temperature superposition (TTS) in studying the rheology of glasses and polymers. It has been reported that the processes involved in molecular relaxation or rearrangements in viscoelastic materials takes place at accelerated rates at higher temperatures. Moreover, there is a direct equivalency between time (the frequency of measurement) and temperature.[2]

Hence, the time over which these processes occur can be reduced by conducting the measurement at elevated temperatures and shifting the resultant data to lower temperatures. The result of this shifting is a "master curve" where the material property of interest at a specific end-use temperature can be predicted over a broad time scale. The amount of shifting along the horizontal (x-axis) in a typical TTS plot required to align the individual experimental data points into the master curve is generally described using

Table 3: Characteristics of the two states of amorphous materials[11]

Glassy state	Rubbery state
Below the glass transition temperature	Above the glass transition temperature
Molecules randomly distributed, liquid-like	Molecules randomly distributed, liquid-like
Low molecular mobility	High molecular mobility
Kinetically stable	Kinetically unstable
Crystallization and chemical reactions are absent or extremely slow	Crystallization and chemical reactions can be observed

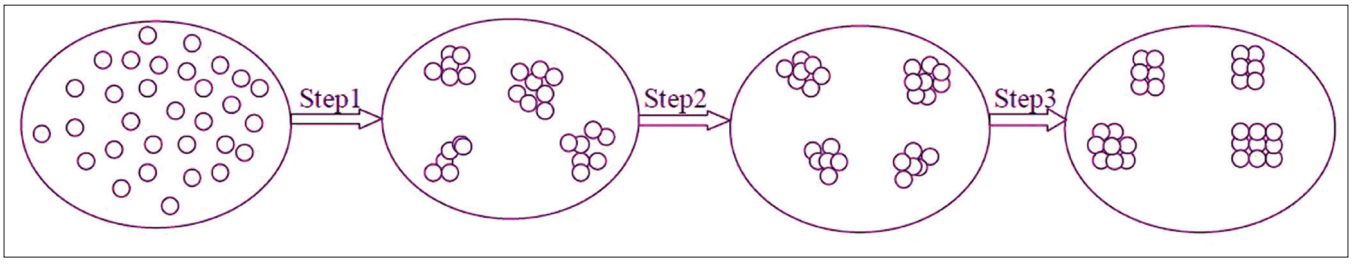

Figure 1: The steps involved in the preparation of solid dispersions

one of two common theoretical models. The first of these models is the Williams–Landel–Ferry (WLF) (Equation 2):[16]

$$\text{Log } A_t = \frac{-C_1 (T-T_0)}{C_1 + (T-T_0)} \quad \text{(Equation 2)}$$

This equation is used for describing the behavior of fragile glasses. C_1 and C_2 are universal constants and T_0 is the reference temperature (in Kelvin), T is the measurement temperature (in Kelvin), and A_t is the shift factor. The WLF equation is typically used to describe the time/temperature behavior of polymers in the glass transition region. The equation is based on the assumption that above the glass transition temperature, the fractional free volume increases linearly with respect to temperature. The model also assumes that as the free volume of the material increases, its viscosity rapidly decreases.

The other model commonly used is the Arrhenius equation (Equation 3)[17]

$$\text{Log } A_t = \frac{E}{C_1 + (T-T_0)} \quad \text{(Equation 3)}$$

where E is the activation energy associated with the relaxation, R is the gas constant, T is the measurement temperature, T_0 is the reference temperature, and A_t is the time-based shift factor. The Arrhenius equation is typically used to describe behavior outside the glass transition region but has also been used to obtain the activation energy associated with the glass transition.[17] Another model used in the rheological study of glassy solids is Vogel Tammann Fulcher (VTF) equation (Equation 4).[11]

$$\tau = \tau_0 \, exp\left(\frac{DT_0}{T-T_0}\right) \text{ and } \eta = \eta_0 \, exp\left(\frac{DT_0}{T-T_0}\right) \quad \text{(Equation 4)}$$

It is used to model the behavior of amorphous solids. T_0 and D are universal constants. T_0 is the temperature at which either τ or η become infinite. D represents the strength parameter.

Classification of amorphous materials

The practical purpose definition of T_g was used by Angell to classify amorphous materials as strong and fragile [Table 4] and plot the logarithms of viscosity and relaxation time as a function of (T_g/T).[12,18,19] In such a plot as in Figure 2, strong materials, i.e., materials that exhibit only small changes in the activation energy for flow with temperature, such as silica, have a nearly linear dependence on the inverse of the reduced temperature, whereas fragile materials deviate strongly from a linear dependence as the activation energies of fragile materials significantly change with temperature. However, this change is characteristic only for intermediate temperatures and the viscosity has Arrhenius type behavior asymptotically both at high and low temperatures. Within the low temperature, the activation energy of viscosity is high Q_H, whereas at high temperatures the activation energy is low Q_L. Doremus suggested to use the ratio (Equation 5).

$$R_D = Q_H/Q_L \quad \text{(Equation 5)}$$

as a fragility criterion.[12,20,21] The higher the value of R_D, the more fragile the material. The fragility of amorphous materials numerically characterized by the Doremus' fragility ratio classifies amorphous materials as strong if they have $R_D < 2$, and fragile materials if they have $R_D \geq 2$.[12]

Antiplasticization

It can be defined as a stabilization mechanism for a solid dispersion in which a matrix with higher glass transition temperature (T_g) is used which reduces the molecularly mobility of the drug and produces a highly stable solid dispersion. Many matrices are hygroscopic and water will be homogenously distributed in the solid dispersion. Water has a very low T_g of 135(K) and it obviously reduces the T_g of the solid dispersion considerably which leads to higher molecular mobility and material will be devitrified. The T_g of such solid dispersions can be predicted with the help of Gordon–Taylor equation (Equation 6);[11,22]

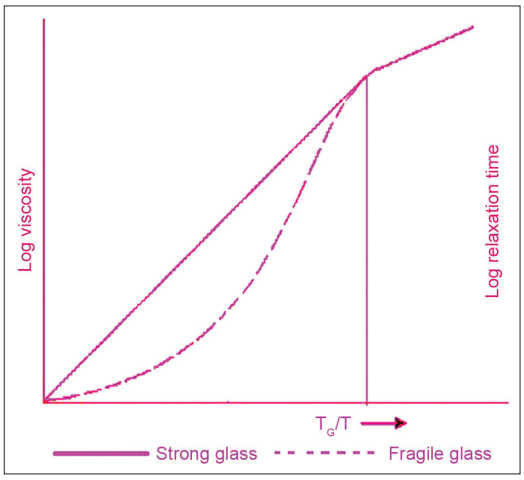

Figure 2: Graphical representation of relationship between viscosity and relaxation time against temperature relative to T_G

Table 4: Angell's classification of amorphous materials[11,18]

Strong glasses	Fragile glasses
Mechanical strength is more	Mechanical strength is lesser
It is more stable	It is less stable
Show Arrhenius behavior	Show non Arrhenius behavior
Follow Arrhenius equation	Follow WLF equation or VTF equation
D values are above 30	D values are less than 10
Undergoes easy vitrification	Vitrification is very difficult
Relaxation time and viscosity decreases slowly in strong glasses	Relaxation time and viscosity decreases more rapidly in fragile glasses
Devitrification or crystallization proceeds at a slower rate	Devitrification or crystallization proceeds at a faster rate
Rarely found in pharmaceutical systems	Commonly found in pharmaceutical systems

$$T_{g,MIX} = \frac{T_{g,D} * W_D + T_{g,C} * K(1 - W_D)}{W_D + K(1 - W_D)}$$

$$T_g, MIX\ T_g, MIX \qquad \text{(Equation 6)}$$

$T_{g, MIX} = T_g$ of solid dispersion.
$T_{g, D} = T_g$ of drug.
$T_{g, C} = T_g$ of matrix
W_D = weight fraction of drug
The constant K is given by the Simha–Boyer rule (Equation 7) as[22]

$$K = \rho D * T_g,D/\rho C * T_g,C \qquad \text{(Equation 7)}$$

ρD = Density of drug

ρ_C = Density of matrix

Drug-polymer ratio[11]

When the drug has a lower T_g than the matrix, a higher drug content decreases the T_g of the solid dispersion and chances of phase separation are increased. Increasing the drug load deteriorates physical stability by altering the T_g of homogenous solid dispersions and also by facilitating crystallization. Increasing the drug load improves physical stability by reducing the plasticizing effect of water and also inhibits phase separation by preventing matrix crystallization. Effects of changing the drug matrix ratio are summarized in Table 5.

Molecular weight of polymer

Development of a stable solid dispersion depends on the minimization of its molecular mobility, and for this purpose matrices with a higher T_g are preferred.[11] A high molecular weight matrix has smaller free volume and thus molecular motions are restricted in such a system. Fox–Flory equation (Equation 8) gives the relation between T_g and molecular weight:[23]

$$1/T_g = 1/T_g^{\infty} + K/DP \qquad \text{(Equation 8)}$$

$T_g^{\infty} = T_g$ at infinite chain length
K = constant depending on monomer geometry
DP = degree of polymerization

Drug–matrix interactions

Drug–matrix interactions determine the physical stability of solid dispersions of solid dispersions during storage. The extend and type of interactions govern the miscibility during fusion, dissolution in common solvent, phase separation, and dissolution of the solid dosage form. Drug–matrix interactions contribute to an increase of T_g than predicted by the Gordon–Taylor equation.[11] Strong interactions present during complex formation increase the T_g and hence increased physical stability.

Table 5: Effects of drug–matrix ratio

Drug matrix ratio	Effects
< 1	• Due to lesser drug contents, the diffusion distance for drug entities is larger and the formation of separate drug phase is retarded • Low drug contents decrease the risk of exceeding the solid solubility which might cause phase separation • Lesser drug- drug contact points and more drug–matrix interaction
> 1	• Higher drug content decrease the hygroscopicity of the solid dispersion and high dosed preparations can be made • Higher drug amount decreases the T_g of the solid dispersion and plasticizing effect of water • It reduces the distance between drug molecules and hence facilitates crystallization and thus decreases stability • Increased drug loads increase the stability of the dispersion by sterically blocking the migration of matrix molecules

Examples:

1. Hydrogen bonding of drugs with poly vinyl pyrrolidone (PVP)[24,25]
2. Photostability of nifidipine and chlorpromazine hydrochloride is increased when incorporated in cyclodextrin cavity.[26,27]

Preparation of Solid Dispersions

Many preparation techniques are currently available for solid dispersions. Phase separation and demixing are the most important problems associated with preparation of solid dispersions.[8] As reported, rapid cooling procedures can reduce the extent of phase separation. The different techniques are as follows:

- Fusion/melting method
- Solvent evaporation method
- Hot melt extrusion method
- Supercritical fluid method
- Miscellaneous method

Fusion/melting method

Fusion method is one of the earliest techniques used for preparation of solid dispersions. First, pharmaceutically applicable solid dispersion was prepared by using this method. Sekiguchi and Obi prepared solid dispersions of sulfathiazole in carriers such as ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide, and urea by melting various drug–carrier mixtures.[8,28-30] It was a eutectic mixture of sulphathizole and urea, which was fused and later cooled to get the final dispersion. The eutectic composition was chosen in order to obtain simultaneous crystallization of drug and matrix during cooling. Polyethylene glycol (PEG) is the hydrophilic polymer commonly used for preparation of solid dispersions. The polymers used generally are

1. Polyethylene glycol (PEG) [MP: 70^{0}C]: Type 3 solid dispersions are produced
2. Poly vinyl pyrrolidone (PVP) [MP: 169^{0}C]: Type 5 and 6 solid dispersions are obtained.

Disadvantages

- The method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature
- Drug and matrix being incompatible results in homogeneous solid dispersions due to formation of two liquid phases
- During cooling, the drug–matrix miscibility changes which eventually results in phase separation
- Degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug.

Solvent evaporation method

The two important steps are

1. A solution containing the matrix and the drug is prepared by proper molecular level mixing with the solvent.
2. Removal of the solvent.[11,28,31]

As the drug and matrix differ comparatively in their polarities, molecular level mixing in a particular solvent becomes very difficult. Another problem is the dispersal of drug and polymer in the finest state as possible to reduce the particle size of the solid dispersion. Use of solubilizers like cyclodextrins and surfactants like tweens are an important strategy to make the drug soluble.[32] The most efficient strategy to increase aqueous solubility of drug is the engaging of a mixture of solvents, for example, water–ethanol, dichloromethane–ethanol.

One of the most important problems associated with the solvent method is the chances of phase separation while solvent removal. Drying at higher temperature speeds up the process and reduces the time available for phase separation. But at higher temperatures the molecular mobility of drug and matrix remains high favoring phase separation. The drying techniques used are summarized in Table 6 and an illustration of a spray drying technique is given in Figure 3.

Hot melt extrusion method

Hot melt extrusion technique was introduced into the pharmaceutical industry as a manufacturing tool around 1970s.[33-36] The basic principle of this technology is similar to that of fusion method except for the employing of extruder for high shear mixing. Literature reports melt extrusion of immiscible components leads to formation of solid dispersion of amorphous drug in a crystalline excipient matrix. The Leistritz twin screw extruder is shown in Figure 4.[37]

Advantages

- Single step preparation of solid dispersions[11]
- Low temperature and shorter residence time of drug–carrier matrix (<2 min)
- Potential to shape the heated drug–matrix mixture into implants, ophthalmic inserts, or oral dosage forms
- Absence of organic solvents and continuous operation
- Greater control on operation parameters and larger scale up possibilities.

Disadvantages

- Miscibility of drug and matrix is the major risk factor
- High shear forces resulting in high local temperatures in the extruder be a problem for heat-sensitive materials.

Supercritical fluid methods

This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursor dyes, and biomolecules such as proteins and peptides.[38] From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug-loaded biopolymer microparticles for pharmaceutical applications has been studied intensively by a number of research groups.[39] In this method, carbon dioxide (CO_2) is used either as a solvent or as antisolvent. Super critical CO_2 is used to dissolve the drug and matrix and

Table 6: Drying techniques used in solvent evaporation method

Drying method	Remarks
Vaccum drying	• Most common method • Solution dried by application of vacuum and moderate heating • At elevated temperatures bears the risk of phase separation
Spray drying	• Solution is dispersed as fine particles in hot air • Larger surface area is offered and the thus the drying is faster • Phase separation is prevented • Yields drug in the amorphous state or sometimes in a partial crystalline state
Freeze drying	• Rarely used for preparation of solid dispersions • Lyophilization process can be sustained only if the solvent has a high vapor pressure • Tertiary butane (TBA) is the only suitable solvent as it has a high melting temperature and high vapor pressure • Drug is subjected to minimum thermal stress • Risk of phase separation is avoided
Spray freeze drying	• Solvent is sprayed into liquid nitrogen and the frozen droplets are lyophilized • Offers the potential to customize the size of particles • Vitrification is faster and the chance for separation is rare

sprayed into an adiabatic expansion vessel and the mixture is cooled rapidly. It is usually referred as the solvent free method or Rapid Expansion of Super Critical Solution (RESS). The applicability of this method is very limited because of the solubility of most pharmaceutical compounds in CO_2 is very less. A schematic representation of the processes involved in supercritical fluid technology is shown in Figure 5. There are many precipitation methods which come under this class. The two reported precipitation methods are

- Gas antisolvent technique (GAS) or precipitation from gas saturated solution (PGSS)
- Precipitation with compressed antisolvent (PCA)

Gas antisolvent technique or precipitation from gas saturated solution

The solution is brought into contact with compressed CO_2. The conditions are chosen such that CO_2 is completely miscible with the solution under supercritical conditions, whereas drug and matrix will precipitate upon expansion of solution. When the volume of solution expands, the solvent strength decreases. This results in precipitation of the matrix and drug. PEG is usually used as the matrix in this method.[40,41]

Precipitation with compressed antisolvent

It involves spraying of a solution containing drug and matrix through a nozzle into a vessel that contains a liquid or supercritical antisolvent. The supercritical antisolvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize, and form particles. Examples of PCA are supercritical antisolvent (SAS) or aerosol solvent extraction system (ASES) and solution enhanced dispersion by supercritical fluids (SEDS).[40,41]

Miscellaneous methods

Evaporative precipitation into aqueous solutions

It is reportedly 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, resulting in solid dispersions of types 4 and 5.[8,42]

Supercritical fluid impregnation

It involves dissolving the drug in a supercritical fluid and exposed to the solid matrix that swells and absorbs the supercritical solution. The diffusion process is controlled by varying the temperature and pressure. The process was reported with poly methyl methacrylate.[8,11]

Electrostatic spinning process

It involves the drug–matrix solution to be pumped through an orifice and then subjected to an electrical field to form fibers of micro- or nanoscale. The fiber diameter can be adjusted by surface tension, electrical field, and dielectric constant.[8,11]

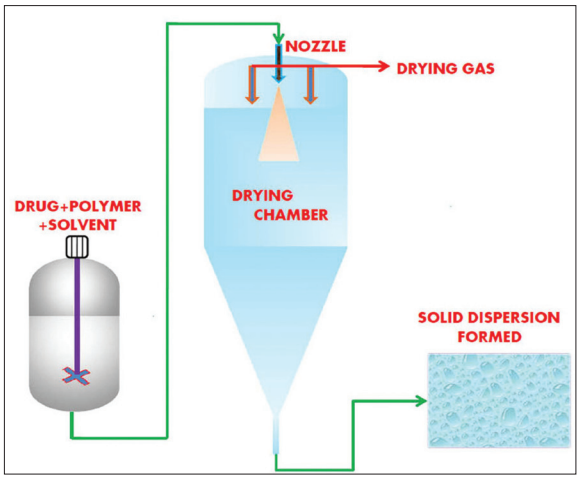

Figure 3: An illustration of a spray drying technique

Figure 4: The leistritz twin screw extruder

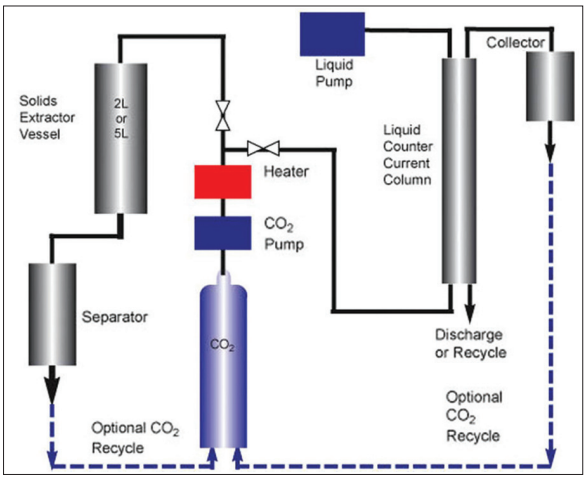

Figure 5: A schematic representation of the processes involved in supercritical fluid technology

Conclusion

The commercial viability of solid dispersion technology is still not cent percent, but it is a promising technology

Table 7: Review of already reported solid dispersions

Drug	Polymer	Method	Reference
Aceclofenac	Polyvinyl pyrrolidone (PVP), Polyethyleneglycol (PEG) 6000, mannitol, urea	Solvent evaporation, physical mixing, fusion	[43]
Valasartan	Gelucire-50/13	Hot melt granulation	[44]
Nimodipine	Plasdone-S630, Eudragit-E100	Hot melt granulation	[45]
Paracetamol	PVP	Kneading technique	[46]
Fluvastatin	PVP, Eudragit-E100, Chitosan	Melt mixing, solvent evaporation	[47]
Aceclofenac	Lactose, mannitol, urea	Solvent evaporation	[48]
Acyclovir	PVP K30, PEG 6000	Solvent evaporation	[49]
Furosemide	Crospovidone	Kneading technique	[50]
Itraconazole	Eudragit-E100	Melt/cool	[51]
Irbesartan	HPMC E5LV	Spray drying	[52]
Magnesium salts	Lecithin,Betaine	Solvent evaporation	[53]
Hydrochlorothiazide	Captopril	Kneading	[54]
Ketoprofen and nifedipine	Ethyl cellulose	Hot melt extrusion	[55]
Verapamil hydrochloride	HPMCK4M, eudragit RSPO	Solvent evaporation	[56]
Gliclazide	PEG 8000	Fusion solvent	[57]
Gliclazide	PEG 6000	Fusion	[58]
Etoricoxib	PVP K30, PEG 4000	Solvent evaporation	[59]
Fenofibrate	PEG 6000, poloxamer 407	Fusion solvent	[60]
Indomethacin	Gelucire-50/13, PEG 4000	Hot melt extrusion	[61]
Pizotifen malate	Povidone	Dissolution , solvent evaporation	[62]
Piroxicam	MCC, potato starch	Co evaporation	[63]
Indomethacin	PEG 6000, myrj 52, lactose, sorbitol, dextrin, eudragit® E100	Solvent evaporation, coevaporation	[64]
Acyclovir	PEG	Hot melt, solvent evaporation	[65]
Glimepiride	PEG4000, HPC or lactose	Solvent evaporation	[66]
Ketoconazole	β–cyclodextrin	Solvent evaporation	[67]
Nimodipine	Ethyl vinyl acetate, Eudragit RL 100, Ethyl acetate	Solvent	[68]
Terbinafine hydrochloride	PEG 6000, PVP K30	Melting and solvent	[69]
Chlordiazepoxide	PVP, Eudragit E100, Mannitol and Sorbitol	Solvent	[70]
Glimepiride	Poloxamer 188 (PXM 18)	–	[71]
Aceclofenac	HPMC, Carbopol 940	Solvent	[72]
Gliclazide	Polyethylene glycol 6000	Fusion	[73]
Bicalutamide	PVPK30	–	[74]
Mk-0591	PVP	–	[75]
Meloxicam	PEG 4000	Dropping	[76]
Allopurinol	PVP K30, PVP K90, PEG 4000, PEG 6000, urea and mannitol	Melting and solvent evaporation	[77]
Diclofenac sodium	Ethyl cellulose, Eudragit, HPMC, Carbomer	Spray drying	[78]
Mebendazole (mbz)	Low-substituted hydroxypropylcellulose (L-HPC)	Lyophilization	[79]
Ofloxacin (ofx)	PEG 4000 or PEG 20000	Solvent	[80]
Indomethacin	Eudragit® RS	–	[81]
Rosiglitazone	PGS, SSG	Dispersion technique	[82]
Simvastatin	PEG 4000, PEG 6000	Fusion technique	[83]
Promethazine Hcl	Eudragit RL100 and S100	Spray drying, freeze drying	[84]
Gliclazide	PEG 4000	Solvent melting	[85]
Celecoxib	PVP-K30	Solvent evaporation	[86]
Ibuprofen	PEG 6000, Poloxomer188 and407	Fusion	[87]
Candesartan cilexetil (CAN)	PEG 6000 and Gelucire 50/13	Melt agglomeration, solvent evaporation	[88]
Valdecoxib (VLB) and etoricoxib (ETB)	PVP	–	[89]
Tolbutamide (TB) and flurbiprofen (FBP)	PVP-K25	Solvent evaporation	[90]
Piroxicam	PVP	Drying and precipitation with compressed Antisolvent	[91]
Glipizide	HPMC	Solvent evaporation	[92]

in advanced drug delivery systems. We have summarized the already reported literatures regarding the formulation of solid dispersion of different drugs in Table 7. Stability, reproducibility, and scale up problems hamper the commercialization of this technique. Availability of new surface active and self-emulsifying carriers extends rays of hope in increasing the commercial feasibility of the technique. Products developed using the surface active carrier technology is available in market. Major focus of future research will be identification of new surface-active carriers and self-emulsifying carriers for solid dispersion. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems.

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