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SOLID DISPERSION: AN OVERVIEW

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Abstract

Solid dispersions have been employed to enhance the dissolution rates of poorly water-soluble drugs. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. In solid dispersion particle size of drug is reduced or a crystalline pure drug is converted into amorphous form and hence the solubility of drug is increased. The review covers concise preface of solid dispersion highlighting various approaches for their preparation, technology involved, selection of carriers and methods of characterization.

1. INTRODUCTION

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration [1-5]. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption [6]. Therefore, pharmaceutical researchers' focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs [7]. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble [8, 9]. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems. It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that potential therapeutic benefits of these active molecules can be realized [10]. 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. Solid dispersion (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method [2, 11]. The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960 [12]. Among the various approaches to improve solubility, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous [13]. Solid dispersion means a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous in nature. Most commonly used carriers for the preparation of SDs are different grade of polyethylene

glycols (PEGs) and polyvinylpyrrolidone (PVPs), Gelucire 44/14, Labrasol, sugars, and urea [14-16]. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [2]. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi [1]. This technique has been used by many researchers/scientists for a wide variety of poorly aqueous soluble drugs to enhance the solubility of the drugs and hence bioavailability [13]. Literature reviews on solid dispersion of past four decades suggests that there is an increasing interest in using this approach [5]. Despite an active research interest, the number of marketed products arising from this approach is really disappointing. Only few commercial products were marketed during the last four decades [1, 17, 18]. Several marketed and late stage drugs are designed for improved solubility by solid dispersion are shown in Table I [1, 17-19]. The goal of review is to highlight the historical background of solid dispersion technology, various preparation techniques with emphasis given to their advantages and disadvantages, commonly used carrier in the preparation of solid dispersions and the recent advances in the field of solid dispersion technology.

2. SOLID DISPERSION

Chiou and Riegelman defined the term solid dispersion as *"a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures"* [2].The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Sekiguchi *et.al.* Suggested that the drug was present in a eutectic mixture in a microcrystalline state [1], after few years Goldberg *et.al.* reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution.[20] Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water

soluble drugs were expected to be high. The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. 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. Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting solvent method. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersion, a first stated by Mayersohn and Gibaldi.

3. ADVANTAGES OF SOLID DISPERSION [21-23]

Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.

Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

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.

4. 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 [24, 25]. Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness [26].

5. TYPES OF SOLID DISPERSION [27]

5.1. Eutectic Mixtures

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly

water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

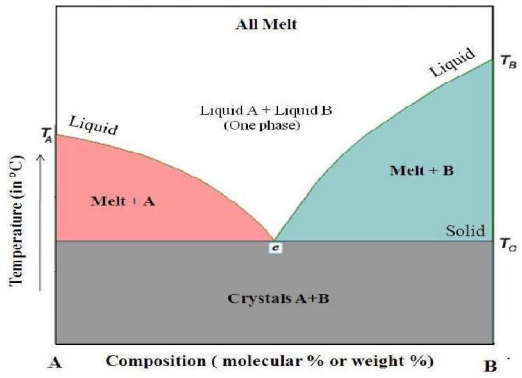

FIG. 1 Phase diagram for a eutectic system

5.2. Solid Solutions

- According to their miscibility two types of solid solution are

Continuous Solid Solutions –

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

Discontinuous Solid Solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram, show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease.

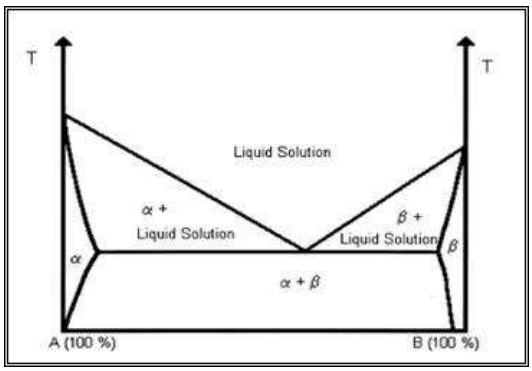

FIG. 2 Phase diagram for a discontinuous solid solution

- According to the way in which the solvate molecules are distributed in the solvendum the two type of solid solution are ---

Substitutional Crystalline Solutions

A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which the solute molecules substitute for solvent molecules in the crystal lattice.

Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

Interstitial Crystalline Solid Solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

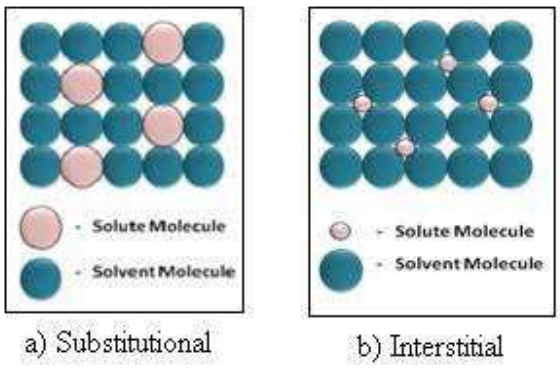

FIG. 3 Substitutional and Interstitial crystalline solid solution

5.3. Amorphous Solid Solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers urea and sugars such as sucrose, dextrose and galactose, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol and various cellulose derivatives have been utilized for this purpose.

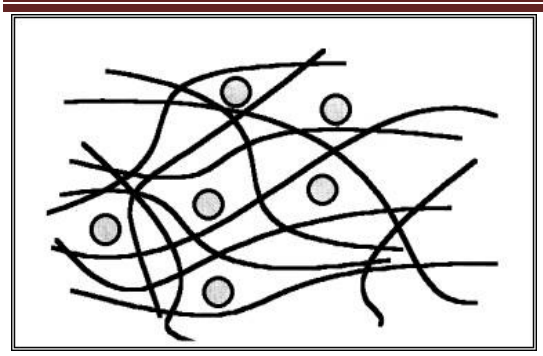

FIG. 4 Amorphous solid solution

5.4. Glass Solutions and Glass Suspensions

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature.

TABLE 1

Types of solid dispersion

No	Solid dispersion type	Matrix *	Drug **	Remarks	No. phases	Ref. to lit.
I	Eutectics	C	C	The first type of solid dispersion prepared	2	(Chiou and Riegelman, 1971)
II	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2	(Breitenbach AH, 2002); (Mullins and Macek, 1960)
III	Solid solutions					
	Continuous solid solutions	C	M	Miscible at all composition, never prepared	1	(Goldberg *et al.,* 1965]
	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed.	2	Sekiguchi K and Obi N (1961)
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that	1 or 2	(Rastogi and Verma, 1956); (Wilcox *et al.*, 1964)

				case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed.		
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2	(Chiou and Riegelman, 1971); (Chiou and Riegelman, 1969)
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2	(Chiou and Riegelman, 1971); (Sarkari M et al., 2002)
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2	(Chiou and Riegelman, 1971); (Sarkari M *et al*., 2002)
VI	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP	1	Simonelli AP *et al*., 1969

*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

6. MECHANISM OF INCREASED DISSOLUTION RATE[28]

The main reasons postulated for the observed improvements in dissolution of these systems are as follows:

a) Reduction of particle size

In case of glass, solid solution and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to an increase in both the surface area solubilization.

b) Solubilization effect

The carrier material, as it dissolves may have a solubilization effect on the drug. This was shown to be the case for acetaminophen and chlorpropamide in urea as well as for numerous other drugs.

c) Wettability and dispersibility

The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media. This should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.

d) Metastable Forms

Formation of metastable dispersions with reduced lattice energy would result in faster dissolution rates. It was found that the activation energies for dissolution for furosemide was 17 K Cal per mol, whereas that for 1:2 furosemide: PVP coprecipitate was only 7.3 K Cal per mol.

7. SELECTION OF A CARRIER

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

1. Freely water-soluble with intrinsic rapid dissolution properties.

2. Non-toxic and pharmacologically inert.

3. Heat stable with a low melting point for the melt method.

4. Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.

5. Able to preferably increase the aqueous solubility of the drug and6. Chemically compatible with the drug and not form a strongly bonded complex with the drug[29].

First generation carriers

Example: Crystalline carriers: Urea, Sugars, Organic acids[30].

Second generation carriers:

Example: Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates.

Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins[31].

Third generation carriers

Example: Surface active self emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14[34]

8. SELECTION OF SOLVENTS[32]

Solvent to be included for the formulation of solid dispersion should have the following criteria:

1. Both drug and carrier must be dissolved.

2. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.

3. Ethanol can be used as alternative as it is less toxic.

4. Water based systems are preferred.

5. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration

Table 2

An overview of common organic solvents[32]

Solvent	Melting point (°C)	Boiling point (°C)	Vapour pressure at 25°C (kPa)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
Chloroform	-63	62	26.1
DMSO	19	189	0.08
Acetic acid	17	118	1.64

9. METHODOLOGIES

The core steps involved in the formation of solid dispersion between a drug and polymer are [33]:

1. Transforming drug and polymer from their solid state to fluid or fluid-like state through processes such as melting, dissolving in solvent or co solvent, or subliming.

2. Mixing the components in their fluid state.

3. Transforming the fluid mixture into solid phase through processes such as congealing, solvent removal, and condensation of sublimed mixture. Basically, there are two methods of preparing solid dispersions, fusion and solvent processes. In case of thermolabile drugs or those with high melting points, a modified method is employed known as melting solvent method. The latter method is limited to drugs with low therapeutic doses, i.e. below 50 mg. However, for the preparation of solid dispersions, several methods have been reported in literature, which are described as under:

9.1.Fusion method

In this method, the carrier is heated to a temperature just above its melting point and drug is incorporated in to the matrix. If the drug has high solubility in the carrier, the drug could remains "dissolved" in the solid state, yielding a solid solution. The melt is solidified in an ice bath under rigorous stirring, pulverized and then sieved. Rapid congealing is desirable, because it results in super saturation of drug as a consequence of entrapment of soluble molecule in the solvent matrix by instantaneous solidification [2]. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix [33] 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.

Advantages

It is more convenient and economical method for drugs stable at temperature below 100^0C Technically it is an easier method if the drug and carrier are miscible in the molten state [2] It precludes the use

an organic solvent thereby circumventing the enigmas of its removal from the dispersion [34]

Dissolution for dispersions obtained by melting technique are much faster than those prepared using solvent techniques [35]

Drawbacks

High melting carrier cannot be used Thermal degradation or instability may result at the melting point [36] Decomposition may take place, often dependent upon composition, fusion time and rate of cooling Evaporation or sublimation and polymeric transformation of the dispersion component may take place [2] Solidified melt may be tacky and unhandable Immiscibility between drug and carrier results in irregular crystallization that causes obvious problems during formulation [37]

9.2 Solvent evaporation technique

Tachibana and Nakamura first reported this method in 1965. This technique involves dissolving the drug and the carrier in a suitable organic solvent or a combination of solvents to get a clear solution. As the solvent is being removed, supersaturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The solvent is then evaporated directly on a water bath or hot plate or using a rota-vapour. The resulting solid dispersion is stored in the desiccator under vacuum and pulverized to obtain the desired size fraction. The important prerequisite for the manufacturing of solid dispersion using the solvent method is that both drug and the carriers are sufficiently soluble in the solvent [5]. Solid dispersion prepared by solvents removal process termed by Bates as coprecipitates [2]. A basic process of preparing solid dispersion of this type consists of dissolving the drugs and the polymeric carrier in a common solvent, such as ethanol, chloroform, or a mixture of ethanol and dichloromethane [34].

Advantages

High melting carries can also be utilized [38], Thermal decomposition of drug and carriers associated with the fusion method can be avoided

Drawbacks

Larger volumes or organic solvent have to be used which makes the process slightly

expensive Removal of the solvent is difficult Residual solvent can have possible adverse effect Difficulty of reproducing crystal forms Supersaturation of the solute cannot b attained unless the system goes through a highly viscous phase

Selection of common solvent is difficult Drug particle size is affected by temperature and rate of evaporation [43]

9.2.1. Types of solvent technique

The choice of solvent and its removal rate are critical to the quality of the dispersion. Depending upon the method of evaporation, there are various types of techniques.

9.2.1.1. Spray drying

Manufacture of milk powder was one of the first applications of spray drying when the method was developed in 1920 [39]. This method consists of dissolving or suspending the drug and carrier, then spraying it in to a stream of heated air flow to remove the solvent [38]. Spray drying usually yields drug in the amorphous state [40], however sometimes the drug may have (partially) crystallized during processing.

Advantages

Ability to work with temperature sensitive APIs. Tremendous formulation flexibility from the wide variety of solvents, polymers and adjuvants that can be employed. Enhancement in performance that can be obtained by mixing the API and polymer at the molecular level in solution and then freezing this morphology in place through rapid solvent removal.

Drawbacks

Added costs associated with the use and consumption of the organic solvents. Requirement of unit operation for residual solvent removal.

9.2.1.2. Freeze drying

To overcome the disadvantages of the above discussed techniques and to obtain a much faster dissolution rate, freeze drying technique has been proposed. The drug and the carrier are dissolved in a common solvent, which is immersed in liquid nitrogen until it is fully frozen then; the frozen solution is further lyophilized. The instance includes that a solid dispersion of tenoxicam with skimmed milk, prepared using freeze drying showed 23-fold increase in solubility with respect to the plain drug.

Advantages

Risk of phase separation is minimized as soon as the solution is vitrified. Offers the potential to customize the size of the particle to make them suitable for further processing.

Drawbacks

The tablets are very fragile.

The manufacturing process is very expensive.

The technique is not suitable for all the products [41]

9.2.1.3. Super critical fluid technology

Super critical fluid technology (SCF) has been introduced in late 1980s and early 1990s. A SCF is a substance that exists above its critical point, which is defined by the conditions of temperature and pressure at which liquid and gaseous states of a substance coexist. When a liquid is heated, its density continues to decrease, while the density of vapor being formed continues to increase. At the critical point, densities of liquid and gas are equal and there is no phase boundary, as shown in Figure 6.

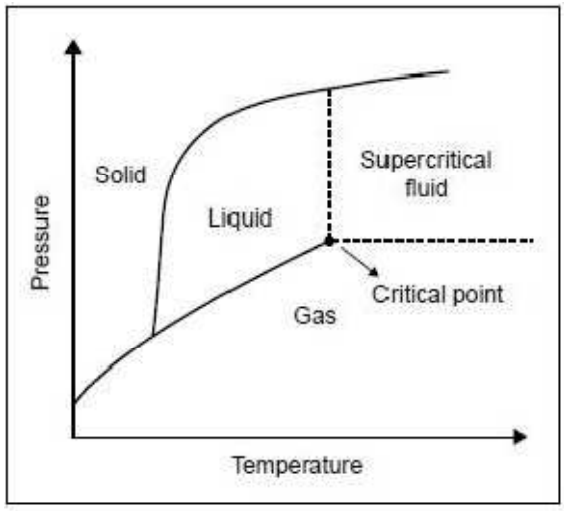

FIG 5: Supercritical region of a hypothetical compound (Indicated by the dotted lines)

Above the critical point that is, in the supercritical region, the fluid possesses the penetrating power typical of a gas and the solvent power typical of a liquid [35, 42].

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an ant solvent. When supercritical CO2 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 does not require the use of organic solvents and since CO2 is considered environmentally friendly, this

technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS).

However, the application of this technique is very limited, because the solubility in CO2 of most pharmaceutical compounds is very low (<0.01 wt-%) and decreases with increasing polarity. Schematic of the RESS apparatus is shown in Figure7 [48-50].

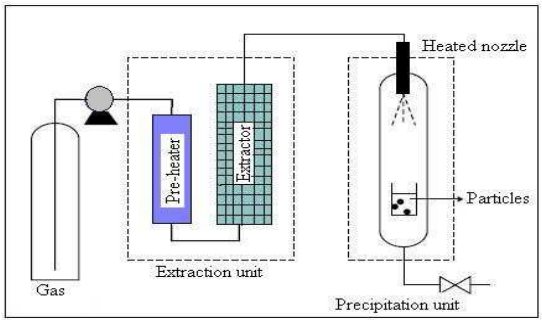

FIG6: Schematic of the RESS apparatus used in supercritical fluid technology

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 CO2. In fact, these techniques represent alternative methods to remove solvents from a solution containing typically a drug and a polymer. One common 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 antisolvent. 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) [51-53].

Advantages

Dissolving power of the SCF is controlled by pressure and/or temperature SCF is easily recoverable from the extract due to its volatility

Non-toxic solvents leave no harmful residue

High boiling components are extracted at relatively low temperatures

Thermally labile compounds can be extracted with minimal damage as low temperatures can be employed by the extraction

Non-inflammable and inexpensive technique [51-53]

Drawbacks

Elevated pressure required

Compression of solvent requires elaborate recycling measures to reduce energy costs

High capital investment for equipment.

9.2.1.4. Co-evaporates

This techniques, drug and copolymer are dissolved separately in same organic solvent and then these two solutions are mixed with further evaporation of solvent under either vacuum or using flash evaporation to give evaporates. Co-evaporates have mainly been employed for dermatological products, e.g., co-evaporates of hydrocortisone acetate-PVP and betamethasone dipropionate-PVP, both of which showed improved ceutaneous penetration [54].

9.2.1.5. Co-precipitates

Co-precipitates are produced by adding a nonsolvent with agitation to a drug and polymer mixture in an organic solvent. The co-precipitates are later filtered and dried.

9.2.1.6. Spin-coated films

It is a new process to prepare solid dispersion by the solvent evaporation method, which consists of dissolving drug and carrier in a common solvent that is dropped on to a clean substrate highly spinned. Solvent is evaporated during spinning. This process is indicated to moisture sensitive drug since it is performed under dry condition [38].

9.3. Solvent melt technique

To overcome the problems associated with fusion technique, a blend of fusion and solvent evaporation method has also been proposed. In this technique, the drug is dissolved in an organic solvent and mixed with the melted carrier. The solvent is then evaporated and the resultant product is pulverized to the desired size.

Advantages

Possesses unique advantages of both the fusion and solvent evaporation methods Useful for thermolabile drugs with high melting point [55].

Drawbacks

Technique is limited to drugs with a low therapeutic dose (less than 50 mg)

9.4. Hot melt extrusion

Hot melt extrusion approach represent the advantageous mean of preparation of solid dispersions by using the twin screw hot

melt extruder where only thermostable components are relevant. The extruder consists of a hopper, barrel, a die, a kneading screw and heaters as shown in Figure 8.

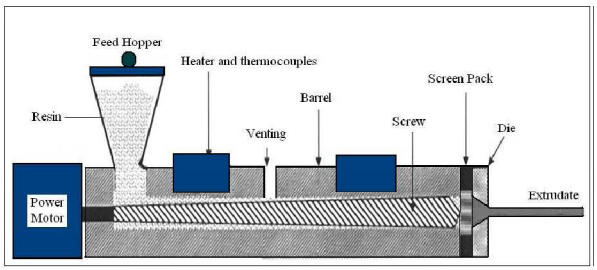

FIG 7: Schematic showing components of a single screw.

Melt extruder

The physical mixture is introduced in to the hopper that is forwarded by feed screw and finally is extruded from the die. The effect of screw revolution speed and water content on preparation of solid dispersions should be investigated, since these parameters have profound impact on the quality of solid dispersions. To reduce the melt viscosity in the extrudate and to be able to decrease temperature settings, a plasticizer can be added to the formulation. Typically, conventional plasticizer suchas triacetin or polyetylene glycol is used in concentration range of 5-30 % weight of the extrudate that lower the processing temperature. Carbon dioxide can act as temporary plasticizer. During extrusion, carbon dioxide is transformed on gaseous phase. As a consequent carbon dioxide escapes from extrudate and does not appear in final product. The role of methylparabene and sorbitol has also been investigated as plasticizer in preparation of sold dispersions in extrusion method [56-59].

This method has been already used to prepare solid dispersions of itraconazole, and hydroxypropylmethylcellulose (HPMC), indomethacin/lacidipine/ nefidipine/ piroxicam/ tolbutamide and polyvinylpyrrolidine(PVP), itrconazole and HPMC 2910/eudragit e100 to improve solubility and dissolution rate of poorly water soluble drugs [44].

Advantages

Possibility of continuous production makes it suitable for large scale production. 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.

Drawbacks

High energy inputs require shear forces and temperature. design of screw assemblies and extruder dies, have significant impact on degradation of drugs and excipients [60]

9.5. Melt agglomeration process

This technique has been used to prepare solid dispersion where the binder acts as a carrier. In addition, solid dispersions are prepared either by heating binder, drug and excipients to a temperature above the melting point of the binder (melt in procedure) or by spraying a dispersion of drug in molten binder on the heated excipients (spray on procedure) by using a high shear mixer. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersions by melt agglomeration. It has been investigated that thespray on procedure with PEG-3000, Poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth.

In addition, the melt in procedure also results in homogeneous distribution of drugs in agglomerate [44].

9.6. Effervescent method

Effervescent solid dispersions incorporate sodium bicarbonate and organic acids (citric, tartaric or succinic), which react with each other to yield an effervescent mixture. By combining poorly soluble drugs with organic acids, one should obtain an effervescent solid dispersion, which may increase the dissolution and absorption rates of poorly soluble drugs. Citric acid/sodium bicarbonate was found to be the most effective carrier for releasing prednisone and primidone and sodium bicarbonate/succinic acid was observed to be the best carrier for griseofulvin. Such dispersion can be made by fusion technique as explained above [61].

9.7. Adsorption on insoluble carriers

These dispersions are also referred to as surface solid dispersions. In this method, the support material is suspended in a solution of the drug followed by evaporation of the solvent. The resulting material contains the drug in a “molecularly micronized” state on the surface of the carrier. Here, adsorbents maintain the concentration gradient (Cs-Ct), to its maximum, thus increasing the dissolution rate. A special technique under these

methods is the fluidized bed system. It involves first preparation of spraying solution by dissolving both drug and carrier and then sugar spheres are charged to fluidized bed granulator and coated. These spheres are fluidized by spraying solution and the coated pellets are dried. Solid dispersion of poorly water-soluble drug nifedipine was prepared in hydroxypropylmethylcellulose (HPMC) on sugar spheres using this technique [62].

9.8. Co-Grinding

In this method, accurately weighed drug powder and the carrier are mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill for grinding. Strong grinding force gives to solid increases in the activation energy on the surface and in the distortion of the crystal lattice together with communition. Boldyrev et al have termed this process as mechanical activation. Some drugs like griseofulvin lose their crystallinity when ground with microcrystalline cellulose in a vibrational ball mill with subsequent increase in dissolution rate and bioavailability [63].

10. CHARACTERIZATION OF SOLID DISPERSION

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion [64].

Drug -carrier miscibility

· Hot stage microscopy

· Differential scanning calorimetry

· Powder X-ray diffraction

· NMR 1H Spin lattice relaxation time

Drug carrier interactions

· FT-IR spectroscopy

· Raman spectroscopy

· Solid state NMR

Physical Structure

· Scanning electron microscopy

· Surface area analysis

· Surface properties

· Dynamic vapor sorption

· Inverse gas chromatography

· Atomic force microscopy

· Raman microscopy

Amorphous content

· Polarised light optical microscopy

· Hot stage microscopy

· Humidity stage microscopy

· DSC (MTDSC)

· ITC

· Powder X-ray diffraction

Stability

· Humidity studies

· Isothermal Calorimetry

· DSC (Tg, Temperature recrystallization)

· Dynamic vapor sorption

· Saturated solubility studies

Dissolution enhancement

· Dissolution

· Intrinsic dissolution

· Dynamic solubility

· Dissolution in bio-relevant media

Powder X-ray diffraction

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

Infrared spectroscopy (IR)

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material [65].

Water vapour sorption

Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different [66]. This method requires accurate data on the hygroscopicity of both

completely crystalline and completely amorphous samples.

Isothermal Microcalorimetry

Isothermal microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg) [67]. This technique has some 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. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

Dissolution calorimetry

Dissolution calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample [68]. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

Macroscopic techniques

Macroscopic techniques that measure mechanical properties that are different amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity for and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additivity of these properties in intimately mixed binary solids.

Differential Scanning Calorimetry (DSC)

Frequently used technique to detect the amount of crystalline material is Differential Scanning

Calorimetry (DSC) [69]. In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

Confocal Raman Spectroscopy

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

Temperature Modulated Differential Scanning Calorimetry (TMDSC)

Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible)are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC [70]. Therefore this technique can be used to assess the amount of molecularly dispersed drug [71]. And from that the fraction of drug that is dispersed as separate molecules is calculated [72].

In Vitro Dissolution Studies

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

Solubility Studies

Solubility studies are done for the finding out the solubility behavior shown by the

solid dispersion system in different types of solvent system and body fluids.

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