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SOLID DISPERSIONS: A REVIEW

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ABSTRACT

Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. This article reviews the various preparation techniques for solid dispersion and compiles some of the recent technology transfers. The different types of solid dispersions based on the molecular arrangement have been highlighted. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterization, along with an insight into the molecular arrangement of drugs in solid dispersions are also discussed. Finally, an in-depth rationale for limited commercialization of solid dispersions and recent revival has been considered.

KEYWORDS: Solid dispersions, carrier, solubility, dissolution, bioavailability.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration, for example, parenteral.

Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Drug absorption from the gastrointestinal

(GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, 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. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. This article focuses on the former, in particular, the use of solid dispersion technologies to improve the dissolution characteristics of poorly water-soluble drugs and in turn their oral bioavailability. Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, Solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water- soluble drugs.

Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption in vivo will be concurrently accelerated with an increase in the rate of drug dissolution. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs (Amidon et al., 1995). Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

With recent advances in molecular screening methods for identifying potential drug candidates, an increasing number of poorly water-soluble drugs are being identified as potential therapeutic agents. In fact, it has been estimated that 40% of new chemical entities currently being discovered are poorly water-soluble (Lipinski, 2001). Unfortunately, many of these potential drugs are abandoned in the early stages of development due to solubility

concerns. It is therefore becoming increasingly more important that methods for overcoming solubility limitations be identified and applied commercially such that the potential therapeutic benefits of these active molecules can be realized.

Definition of solid dispersions

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.

Advantages of solid dispersion

1. 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 solublecarriers.

Table 1: Types of Solid dispersion.

Solid dispersion type		Matrix*	Drug**	Remarks	No. phases	Ref. to lit.
1.	Eutectics	C	C	The first type of solid dispersion Prepared	2	(Chiou and Riegelman, 1971)
2.	Amorphous Precipitations in crystalline matrix	C	A	Rarely encountered	2	(Breitenbach AH,2002); (Musllins and macek,1960)
3.	Solid solutions					
4.	Continuous solid Solutions	C	M	Miscible at all composition, never Prepared	1	(Goldberg *et al.*,1965)
5.	Discontinuous solid solution	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed	2	Sekiguchi K and Obi N (1961)
6.	Substitutional solid solution	C	M	Molecular diameter of drug (Solute) differ less than 15% from the matrix (solvent) diameter. in that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed	1 or 2	(Rastogi and Verma, 1956); (Wilcox *et al.*, 1946)
7.	Interstitial solid Solution	C	M	Drug (solute) molecular diameter Less than 59% of matrix (solvent) diameter. Usually limited miscibility Discontinuous. Example: Drug in helical interstitial space of PEG.	2	(Chiou and riegelman,1971)
8.	Glass suspension	A	C	Partical size of dispersed phase dependent on cooling/evaporation rate. Obtained after the crystallization of drug in amorphous matrix.	2	(Chiou and Riegelman, 1971); (Sarkari M *et al.*,2002)
9.	Glass suspension	A	A	Partical size of dispersed phase dependent on cooling/evaporation Rate many solid dispersion are of this type.	2	(Chiou and Riegelman, 1971); (Sarkari M *et al.*,2002
10.	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 is dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix

A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

2. 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 (Sekiguchi and Obi, 1964) 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 (Pouton, 2006 and Kang et al., 2004).

3. Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity (Vasconcelos and Costa, 2007). 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 (Ghaderi et al., 1999). The increased porosity of solid dispersion particles also hastens the drug release profile.

4. Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility (Pokharkar et al., 2006 and Lloyd et al., 1999). 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 (Taylor and Zografi, 1997). 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 (Leuner and Dressman, 2000, Karavas et al., 2006).

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.

Preparation of solid dispersions

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete), and formation of different phases is 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 procedure (Chiou and Riegelman, 1971, Sekiguchi and Obi, 1961). Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation is prevented by maintaining the driving force for phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

A Fusion method

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix (Sekiguchi and Obi, 1961) 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. This procedure resulted in solid dispersions of type I. Poly(ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG. The helices are aligned in orderly fashion, illustrating that PEG easily crystallizes. Another polymer frequently applied as a matrix in the fusion method is poly (vinyl pyrollidone) PVP. PVP, supplied in the amorphous state, is heated to above its Tg (glass transition temperature). The drug has to fuse with or dissolve in the rubbery matrix, which is subsequently cooled to vitrify the solid dispersion. When PVP is used as matrix, solid dispersions of type V or VI are obtained. The mode of incorporation of the drug

depends on the PVP-drug miscibility and the preparation procedure. Grinding is required to obtain the solid dispersion as powder that is easy to handle.

Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture (Greenhalgh et al., 1984 and Timko and Lordi, 1984), which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants (Damian et al., 2002 and Vippagunta et al., 2002).

Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions (Save and Venkitachalam, 1992 and McGinity et al, 1984). Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug. For example, to melt a sugar matrix of galactose a temperature of 169°C was required (Allen et al., 1977) and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. Poly ethylene glycols melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method.

B. 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. When compared to melting in a vessel, the product stability and dissolution are similar (Forster et al., 2001), but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms (Breitenbach, 2002). Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are 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 be a problem for heat sensitive materials (Langer et al., 2003 and Forster et al., 2001). 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.

C. Solvent method

The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges.

The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible (Hernandez-Trejo et al., 2005), preferably drug and matrix material are in the dissolved state in one solution.

Various strategies have been applied to dissolve the lipophilic drug and hydrophilic matrix material together in one solution. Low drug concentrations are used to dissolve both drug and matrix material in water (Orienti, et al., 2002), but this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical. Solubilisers like cyclodextrins or surfactants like Tween80® increase the aqueous solubility of the drug substantially. However, the amount of solubilisers or surfactants in the final product are often eminent. This results in solid dispersions that, to a significant extent, consist of solubilisers or surfactants, materials that significantly change the physical properties of the matrix (e.g., decrease of 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 (Betageri and Makarla, 1995) or dichloromethane (Damian et al., 2002) have been used to dissolve both drug and PVP as matrix simultaneously. These solvents are used also in other preparation methods. However, according to the ICH-Guidelines, these solvents belong to Class I, comprising the most toxic solvents. Therefore, the use of these solvents is unacceptable and impractical because 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 (Kushida et al., 2002), or dichloromethane and ethanol (Cilurzo et al., 2002) 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 temperatures speeds up the process and reduces the time available for phase separation. On the other hand, at high temperatures the molecular mobility of drug and matrix remains high, favoring phase separation (e.g., crystallization). This is depicted in fig. 1.

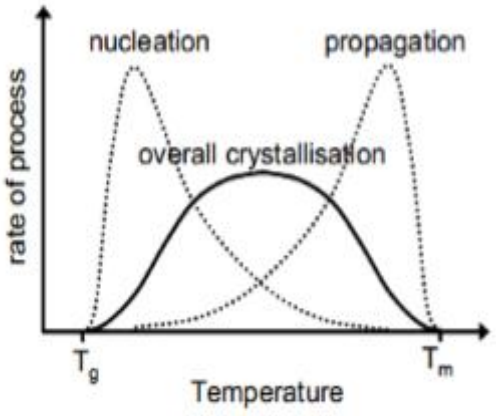

Fig. 1: Overall crystallization rate as a function of temperature. Tg is the glass transition temperature and Tm is the melting temperature. Adapted from (Slade and Levine, 1991).

To dry the solutions, vacuum drying is often used (Langer et al., 2003). The solution is dried by the application of vacuum and moderate heating. Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. Afterwards the formed solid dispersion is often stored in a vacuum desiccator to remove the residual solvent. Vacuum drying at elevated temperature bears the risk of phase separation because the mobility of drug and matrix decreases slowly. Another drying technique is spray drying. The solution is dispersed as fine particles in hot air. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Moreover, the solid dispersions prepared by spray drying consist of particles of which the size 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 (Paradkar et al., 2004), however sometimes the drug may have (partially) crystallized during processing (Weuts et al., 2005).

An alternative to these drying techniques is freeze drying. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in

stabilizing matrices (Eriksson et al., 2002), the technique is poorly exploited for the preparation of solid dispersions (Sethia and Squillante, 2003 and Yoo et al., 2000). One of the reasons might be the low freezing temperature of most organic solvents (table 2) Obviously, sublimation during freeze drying is only possible when the solvent stays frozen. In addition when the formation of a glass is envisaged, the sample temperature should be kept below the Tg of the maximally freeze concentrated fraction. Therefore, low sample temperatures are required which slows down the process. Betageri and Makarla, 1995 used a condenser temperature of -75°C, to dry a solution with cyclohexanol as the solvent. In table 2 an overview is presented of several organic solvents. To obtain a lyophiliation process of acceptable duration, the solvent should have a sufficiently high vapour pressure.

Table 2: Over view of some organic solvent.

Solvent	Melting Point (ºC)	Boiling Point (ºC)	Vapour pressure At 25ºC (kPa)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
1-propanol	-85.8	97.4	2.27
2-propanol	-127	82.4	5.85
Chloroform	-63	62	26.1
Dimethylsulphoxide(DMSO)	19	189	0.08
Acetic acid	17	118	1.64
1,4-dioxane	12	102	4.92
2-methyl-2-propanol (TBA)	25	82	5.49

As can be seen in table 2, dimethylsulphoxide (DMSO) has a high melting temperature but it has a very low vapour pressure. Therefore, DMSO is not suitable as a solvent for freeze drying.

A suitable solvent that meets both requirements is 2- methyl-2-propanol or tertiary butanol (TBA), because it has a high melting temperature as well as a high vapour pressure. The application of TBA in lyophilization is discussed by Teagarden (Teagarden and Baker, 2002). Also mixtures of solvents can be considered. For example, while water and DMSO have melting points of 0°C and 19°C, the mixture has eutectic points below - 60°C. The sample temperature of such a mixture should be kept below this value, which causes a slow sublimation.

An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of

freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum (Costantino et al., 2002; Johnston and Williams, 2004; Leuenberger, 2002). Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary (Maa et al., 1999), or nasal administration (Maa et al., 2003).

In an electrostatic spinning process a drug-matrix solution is pumped through an orifice and then subjected to an electrical field to form fibres 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 fibre forming materials. The fibre diametercan be adjusted by surface tension, electrical field and dielectric constant (Sethia and Squillante, 2002). After rapid evaporation of the solvent, the fibres can be directly used or milled and further processed (Verreck et al., 2003).

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, resulting in solid dispersions of type IV/V. It was concluded that the amorphous state of the drug was best preserved with the spray freeze drying process (Sarkari et al., 2002).

D. Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an anti-solvent (Kompella and Koushik, 2001; Palakodaty and York, 1999). 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 (<0.01wt-%) (Subramaniam et al., 1997) and decreases with increasing polarity. Therefore, scaling up this process to kilogram-scale will be impractical.

All other supercritical techniques are precipitation methods. Although generally labelled 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, thesetechniques represent alternative methods to remove solvents from a solution containing typically a drug and a polymer. Moneghini and co-workers (2001) 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). The solution is brought into contact with compressed CO2. The conditions are chosen so that CO2 is completely miscible with the solution under supercritical conditions, whereas 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. This results in precipitation of matrix and drug. Since this technique is often applied with PEG as matrix, this technique results in formation of a solid dispersion with a crystalline matrix (Sethia and Squillante, 2002).

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) (Subramaniam et al., 1997). More specific examples of PCA are Supercritical AntiSolvent (SAS) when supercritical CO2 is used, or Aerosol Solvent Extraction System (ASES), and Solution Enhanced Dispersion by Supercritical fluids (SEDS) (Kompella and Koushik, 2001; Subramaniam et al., 1997). However, as with the other solvent techniques described in the previous section, the critical step in these precipitation techniques might be the dissolution of drug and matrix in one solution. The use of water is limited, because the water solubility in compressed CO2 is limited (Sarkari et al., 2002). Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix (Sethia and Squillante, 2002).

In another process called supercritical fluid impregnation,

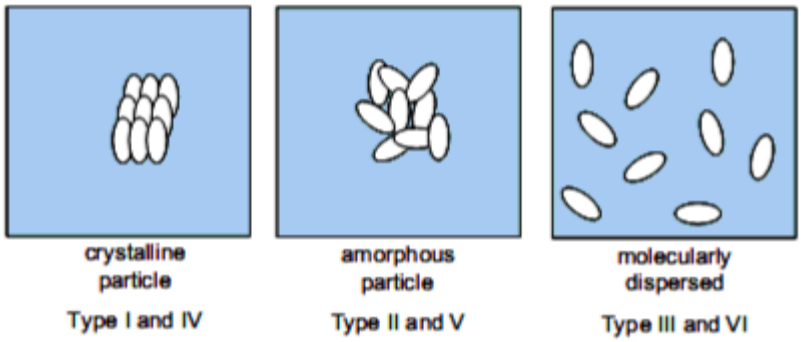

Fig. 2: Schematic representation of three modes of incorporate of the drug in a solid dispersion.

The drug is dissolved in a supercritical fluid and exposed to solid matrix material that swells and absorbs the supercritical solution. By varying the pressure and the time of exposure, the diffusion process can be controlled. The absorption stops when the pressure is reduced. This process is investigated for poly (methyl methacrylate) (Vincent et al., 1997) but can be applied for other polymers as well.

Characterization of solid dispersion

A. Detection of crystallinity in solid dispersions

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions (fig. 2).

Many attempts have been made to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. For that purpose many techniques are available which 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 (Kaushal et al., 2004). It should be noted that through the assessment of crystallinity as method to determine the amount of amorphous drug it will not be revealed 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 can be used to qualitatively detect material 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 (Forster et al., 2001). Sharp vibrational bands indicate crystallinity (Bugay, 2001). Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99% in pure material (Taylorand Zografi, 2001). However in solid dispersions only qualitative detection was possible (Broman et al., 2001).
3. Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different (Buckton and Darcy, 1995). This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.
4. Isothermal Microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg) (Sebhatu et al., 1994). However, 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.
5. Dissolution Calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample (Pikal et al., 1978). Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.
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 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.
7. A frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC) (Kerc and Srcic, 1995). 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. Possibly, the recrystallization 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.

B. 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 behaviour could be different for solid dispersions that do not contain any crystalline drug particles, i.e. solid dispersions of type V and VI or for type II and III. 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.

1. Confocal Raman Spectroscopy was used to measure the homogeneity of the solid mixture of ibuprofen in PVP (Breitenbach et al., 1999). It was described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the pixel size of 2 µm3, uncertainty remains about the presence of nano-sized amorphous drug particles.
2. Using IR or FTIR, the extent of interactions between drug and matrix can be measured. The interactions are indicative for the mode of incorporation of the drug, because separately dispersed drug molecules will have more drug-matrix interactions than when the drug is present in amorphous clusters or other multi-molecule arrangements (Li et al., 2002; Rogerset al., 2002).
3. 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 (DeMeuter et al., 1999). Therefore this technique can be used to assess

the amount of molecularly dispersed drug (Cilurzo et al., 2002), and from that the fraction of drug that is dispersed as separate molecules is calculated (Vasanthavada et al., 2004).

Unmet needs and challenges

In spite of almost several years of research on solid dispersions, their commercial application is limited. Only a few products have been marketed so far. Amongst these are:

1) Gris-PEG (Novartis), griseofulvin in PEG
2) Cesamet (Lily), nabilone in PVP
3) Sporanox (Janssen Pharmaceutica/J&J), itraconazole in HPMC and PEG 20,000 sprayed on sugar spheres.

The limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations include:

1. Laborious and expensive methods of preparation,
2. Reproducibility of physicochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms,
4. Scale-up of manufacturing process, and
5. Stability of the drug and vehicle.

Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. Some of the suggested approaches to overcome the aforementioned problems and lead to industrial scale production are discussed here under alternative strategies.

Alternative strategies

A. Spraying on sugar beads using a fluidized bed coating system

The approach involves a fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granules ready for tableting or drug-coated pellets for encapsulation in one step. The method has been applied for both controlled- and immediate-release solid dispersions. (Beten et al., 1995; Ho Ho et al., 1996).

Itraconazole (Sporanox oral capsules, Janssen Pharmaceutica, Titusville, NJ) coated on sugar sphere, is made by layering onto sugar beads a solution of drug and hydroxypropylmethylcellulose (HPMC) in an organic solvent of dichloromethane and ethanol

(Gilis et al., 1997). A solid solution of drug in HPMC is produced upon coating (cosolvent evaporation) and controlled drying of coated beads in a closed Wurster process. As this thin film dissolves in water or gastric fluid, the molecularly dispersed itraconazole is released at supersaturated concentration. HPMC acts as a stabilizer to inhibit recrystallization of the itraconazole. The supersaturated solutions of itraconazole are sufficiently stable to allow for absorption and distribution.

B. Direct capsule filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. The filling of hard gelatin capsules has been feasible in molten dispersions of Triamterene-PEG 500 using a Zanasi LZ 64 capsule- filling machine (Zanasi Co., Bologna, Italy) (Walker et al., 1980). However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug (Serajuddin et al., 1988). A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (eg, polysorbate 80 with PEG, phosphatidylcholine with PEG) (Serajuddin et al, 1990; Law et al., 1992). The temperature of the molten solution should not exceed ~70oC because it might compromise the hard-gelatin capsule shell.

C. Electrostatic spinning method

This technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology (Reneker, 1993; Reneker and Chun, 1996). This technology is now applied in the pharmaceutical field. (Ignatious and Baldoni, 2001).

In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. 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 mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength (Deitzel et al., 2001).

Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and non- biodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by water-soluble carriers could be

used in oral dosage formulations by direct incorporation of the materials into a capsule. Itraconazole/HPMC nanofibers have been prepared using this technique (Verreck et al., 2003).

D. Surface-active carriers

The surface-active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs have been of great interest in recent years. A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs.

Two of the important surface-active carriers are Gelucire 44/14 and Vitamin E R-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Gelucire 44/14 (Gattefosse Corp, Gennevilliers, France) has commonly been used in solid dispersion for the bioavailability enhancement of drugs. (Dennis et al., 1990; Pozzi et al., 1991); Sheen et al., 1995; Porter et al., 1996). Gelucire 44/14 is a mixture of glyceryl and PEG 1500 esters of long-chain fatty acids and is official in the European Pharmacopoeia as lauryl macrogolglycerides; the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophilic-lipophilic balance (HLB) value. Vitamin E TPGS National Formulary (NF) (Eastman, Kingsport, TN) is prepared by the esterification of the acid group of d-R- tocopheryl acid succinate by PEG 1000. The material has an HLB value of 13 and is miscible with water in all parts. Its melting point, however, is relatively low (38oC), and it may require mixing with other carriers to increase melting temperatures of formulations.

A commonly used surfactant, Polysorbate 80, when mixed with solid PEG, has also been reported to be an alternative surface-active carrier (Morris et al., 1992). Polysorbate 80 is liquid at room temperature; it forms a solid matrix when it is mixed with a PEG because it incorporates within the amorphous regions of PEG solid structure. As much as 75% (wt/wt) Polysorbate80 was incorporated, PEG remained semisolid, and the lowering of the melting temperature of the PEG used was <12oC(Morris KR et al., 1992) The PEG-polysorbate carriers have been found to enhance dissolution36 and bioavailability (Porter et al., 1996) of drugs from the solid dispersions. Incorporation of 5% (wt/wt) phosphatidyl- choline resulted in enhanced dissolution rate of nifedipine from a PEG-based solid dispersion. Pulverized solid dispersions in PEG containing varying amounts of ionic and nonionic surfactants, including sodium dodecyl sulfate and Polysorbate 80 gave increased dissolution rate of drug (Sjokvist et al., 1992).

A solid dispersion of poorly soluble REV5901 in Gelucire 44/14 under a fasting regimen had much higher bioavailability in human volunteers than that of a tablet formulation even though the micronized form of drug and a wetting agent were used in the tablet (Sheen et al., 1991). The bioavailability of ubidecarenone in dogs from solid dispersion in Gelucire 44/14 and the Gelucire 44/14- lecithin mixture were 2 and 3 times higher, respectively, than that of commercially available tablet (Pozzi et al., 1991).

CONCLUSION

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling.

Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

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