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A review on solid dispersionSameer Singh^{1*}, Raviraj Singh Baghel² and Lalit Yadav³

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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 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. The focus of this review article on advantages, disadvantages and the method of preparation, and characterization of the solid dispersion.

Key-Words: Solubility, Solid Dispersions, Carrier, Bioavailability

Introduction

The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited gastrointestinal absorption generally show improved dissolution and bio availability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which results in poor wettability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubalization by cosolvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles.

The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. solid dispersion technique was firstly demonstrated by Sekiguchi and Obi. They proposed the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carries like urea. Upon exposure to aqueous fluids the active drug released into fluids is fine, dispersed particles because of fine dispersion of the drug in the solid eutectic mixture and the faster dissolution of the soluble matrix. The eutectic mixture contained 52 per cent w/w of sulfathiazole and 48 per cent w/w of urea. The possibility of using solid solution approach in which a drug is molecularly dispersed in soluble carrier was subsequently introduced.

A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961). Technique for the preparation of solid dispersions, Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980).¹

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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.

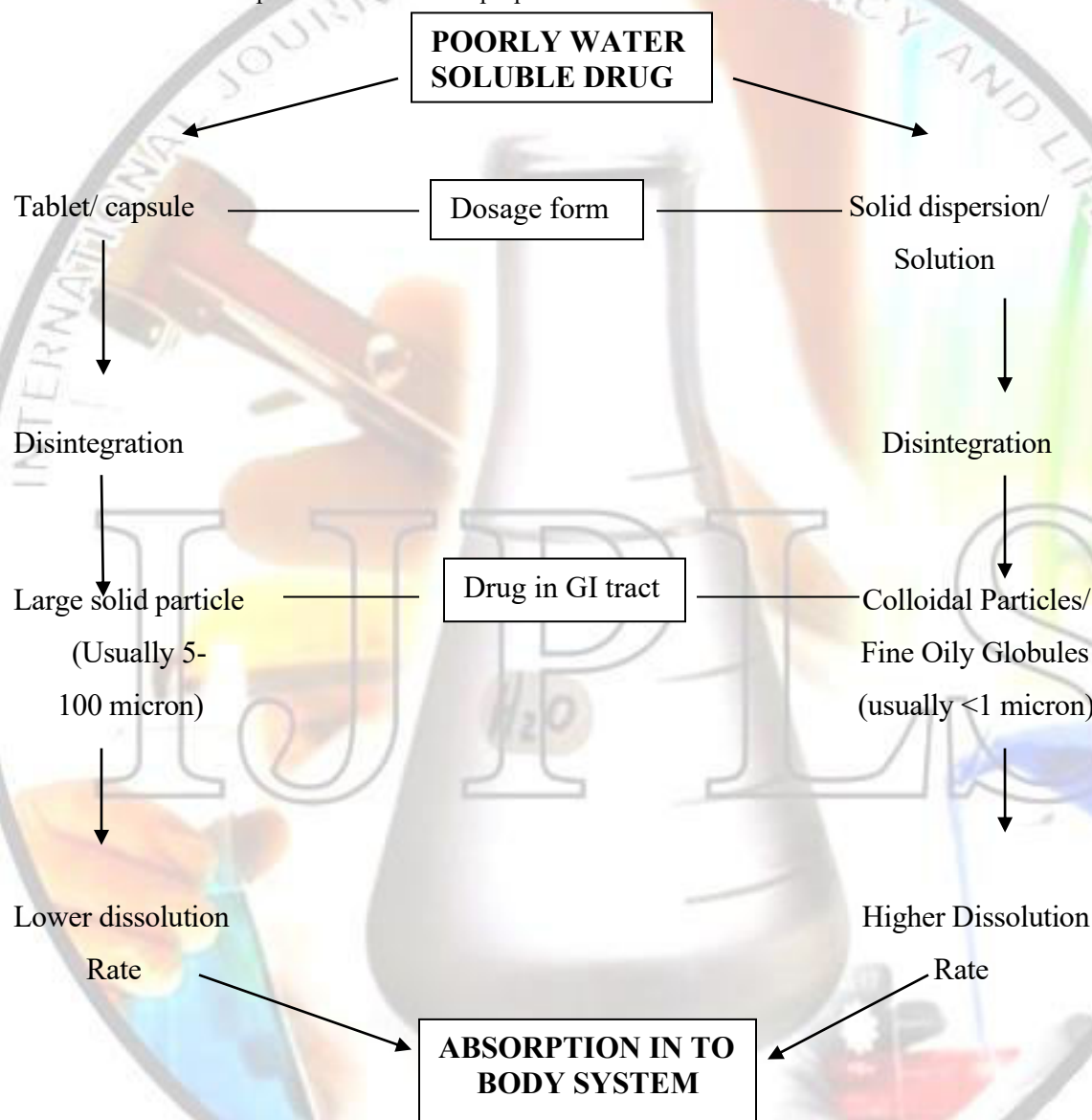


Fig.. 1: A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. 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 it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method⁴. The technique has been used for a wide variety of poorly aqueous soluble drug.

Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Noyes-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.^[1,2]

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h}$$

Where, dC/dt - is the rate of dissolution, A - is the surface area available for dissolution, D - is the diffusion coefficient of the compound, C_s - is the solubility of the compound in the dissolution medium, C - is the concentration of drug in the medium at time t and h - is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

To increase the dissolution rate from equation the following approaches are available.

- To increase the surface area available for dissolution. Decreasing the particle size of drug.
- Optimizing the wetting characteristics of compound surface.
- To decrease the boundary layer thickness.
- Ensure sink condition for dissolution.
- Improve apparent solubility of drug under physiologically relevant conditions.
- Drug administered in fed state is a way to improve the dissolution rate.

Of these possibilities, changes in the hydrodynamics are difficult to invoke *in-vivo* and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the luminal fluids. Although some research effort has been directed towards permeability enhancement using appropriate

excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media.^[3]

The approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general, include micronization, salt formation, use of surfactant and use of pro-drug^[5], however all these techniques have certain limitations. Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions. Chiou and Riegelman outlined 6 types of drug carrier interactions in solid-state dispersions: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates, and compound or complex formation. Other factors such as increased wettability, solubilization of the drug by the carrier at the diffusion layer, and the reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. Micronization has several disadvantages, the main one being the limited opportunity to control important characters of the final particle such as size, shape, morphology, surface properties and electrostatic charges. In addition micronization is a high-energy process, which causes disruptions in the drug's crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. The amorphous regions are thermodynamically unstable and are therefore susceptible to recrystallization upon storage, particularly in hot and humid conditions^[6-8]. All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. The dissolution rate of a particular salt is usually different from that of parent compound. However sodium and potassium salts of weak acids dissolve more rapidly than the free salts. Potential disadvantages of salt forms include high reactivity with atmospheric carbon dioxide and water resulting in precipitation of poorly water-soluble drug, epigastric distress due to high alkalinity.

Use of co-solvents or surfactants to improve dissolution rate pose problems, such as patient compliance and commercialization. Even though particle size reduction increases the dissolution rate, the formed fine powders showing poor wettability and flow properties. Solid dispersion technique has come into existence to eliminate all these problems. However, the most attractive option for increasing the

release rate is improvement of the solubility through formulation approaches. [9, 10]

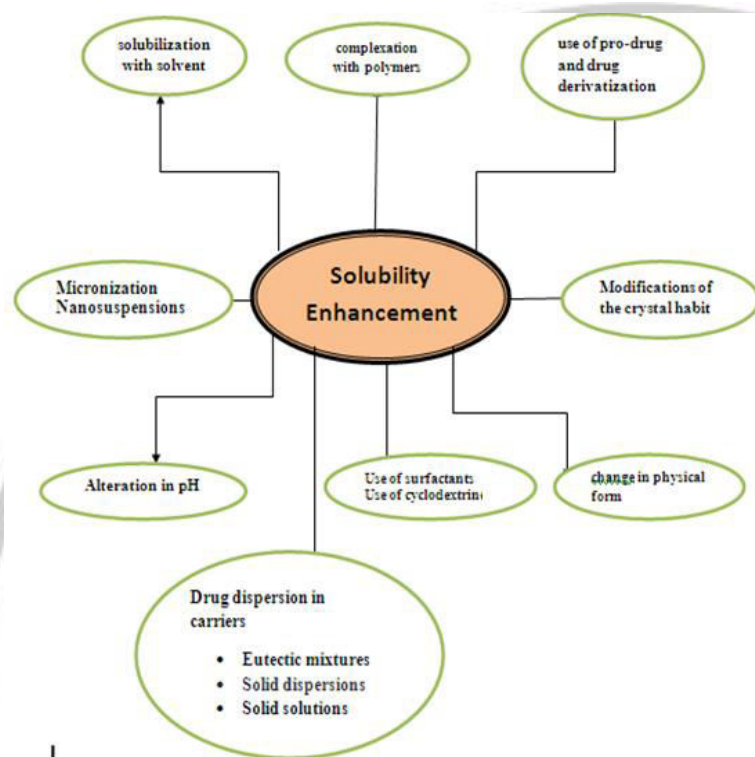


Fig. 2: Summarizes the various formulation and chemical approaches that can be taken to improve the solubility or to increase the available surface area for dissolution.

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” [11].

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 [8], 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.[5] 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.

Classification of solid dispersion

Based on their molecular arrangement, six different types of solid dispersions can be distinguished. (In Table 1.1) Moreover, in various studies the designation of solid dispersions is based on the method of preparation. However, since different preparation methods can result in the same subtypes or similar preparation methods can result in different subtypes, it can be argued that solid dispersions should preferably be designated according to their molecular arrangement. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions. Therefore, it is essential to use terms that indicate the molecular arrangement in the solid dispersion. Knowledge about the molecular arrangement will enlarge comprehension of the properties and behavior of solid dispersions. Furthermore, it will facilitate optimization of their properties required for a specific application [12].

For example, the mechanism underpinning the dissolution of solid dispersions is poorly understood. Many case studies showed accelerated dissolution of hydrophobic compounds using solid dispersions but mechanisms are rarely discussed. The most important reason for that is the lacking knowledge about the mode of incorporation of the hydrophobic drug in the matrix, despite numerous efforts to clarify this. A

question like, “is the drug present as a crystalline phase or as amorphous nano-particles or molecularly dispersed throughout the matrix” is rarely discussed^[13]. All three situations result in different drug concentrations at the dissolving interface. Still it has not been fully elucidated how this affects dissolution behaviour of solid dispersions. Secondly, the physical and chemical stability of the matrix or the incorporated

drug depends on the mode of incorporation. If drug molecules, for example, are present in amorphous nano-particles, crystallization requires only rotational rearrangement. On the other hand, for a molecularly dispersed drug, translational diffusion is necessary before crystallization can occur by rotational rearrangements.

Table 1.1: Classification of solid dispersions in six subtypes

SOLID DISPERSION TYPE	matrix *	drug **	remarks	no. phases
I eutectics	C	C	the first type of solid dispersions prepared	2
II amorphous precipitations in crystalline matrix	C	A	rarely encountered	2
III solid solutions				
continuous solid solutions	C	M	miscible at all compositions, never prepared	1
discontinuous solid solutions	C	M	partially miscible, 2 phases even though drug is molecularly dispersed	2
substitutional solid solutions	C	M	molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed	1 or 2
interstitial solid solutions	C	M	drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2
IV glass suspension	A	C	particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
V glass suspension	A	A	particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
VI glass solution	A	M	requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP	1
Related and other designations				
complex formation	C/A	M	drug and matrix strongly interact and form complexes in aqueous environment. e.g. cyclodextrins or solid surfactants	1
monotectics	C	C	same as eutectics but eutectic melting convergent with pure material, for completely non-interacting systems	2
co-precipitates	?	?	prepared by addition of non-solvent to solution of drug and matrix	?
co-evaporates	?	?	prepared by vacuum drying, spray drying, freeze drying and spray-freeze drying, many examples	?

*A: matrix in the amorphous state, C: matrix in the crystalline state, **A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix

The physical state of the matrix is also important for the chemical stability of the drug. The crystallinity of the matrix influences the translational and rotational

rearrangements of the drug necessary for degradation reactions. Finally, then influence of drug load and method of preparation on dissolution behavior and stability of solid dispersions can only be understood and predicted when the relation between these characteristics and the mode of incorporation is known.^[14]

Current trends in solid dispersions techniques

New manufacturing processes to obtain solid dispersions have also been developed to reduce the drawbacks of the initial process. It is intended to discuss the recent advances related on the area of solid dispersions. The classification of solid dispersions according to implementation and recent advancement [15]

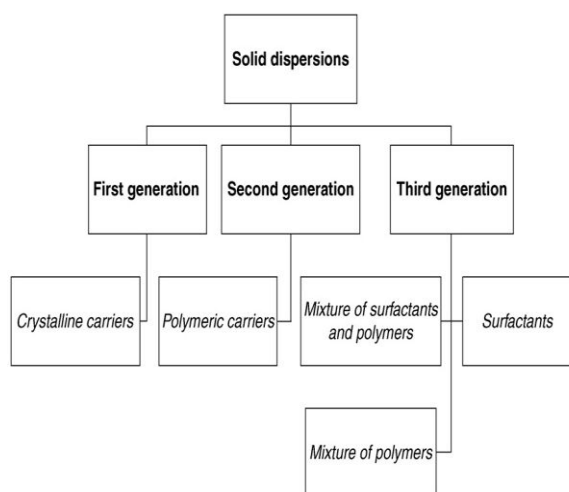


Fig. 3: The classification of solid dispersions.

First generation solid dispersions

The first description of solid dispersions was from Sekiguchi and Obi in 1961. They noted that the formulation of eutectic mixtures improves the rate of drug release and consequently, the bioavailability of poorly water soluble drugs. In the same decade, several solid dispersions were described using poorly water soluble drugs, such as sulfathiazole [17] and chloramphenicol [16] using urea as high water soluble carrier. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs. The small particle size and the better wettability of the drug were the main reasons for the observed improvements in bioavailability.

Later, Levy [18] and Kaning [19] developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. The observed improvements were attributed to a faster carrier dissolution, releasing microcrystals or particles of drug [21]. These solid dispersions, which could be designed as first generation solid dispersions, were prepared using crystalline carriers. Crystalline carriers include urea [16, 17] and sugars [19], which were the first carriers to be employed in solid dispersions. They have the disadvantage of forming crystalline solid dispersions,

which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

Second generation solid dispersions

In the late sixties it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically stable [21-23]. Therefore, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. Indeed, the most common solid dispersions do not use crystalline carriers but amorphous. In the latter, the drugs are molecularly dispersed in an irregular form within an amorphous carrier, which are usually polymers [24]. Polymeric carriers have been the most successful for solid dispersions, because they are able to originate amorphous solid dispersions. They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP) [25-30], polyethyleneglycols (PEG) [23,31-33] and polymethacrylates [34,35]. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose [39] or starch derivatives, like cyclodextrins [36-41]. Amorphous solid dispersions can be classified according to the molecular interaction of drug and carriers in solid solutions, solid suspensions or a mixture of both [26]. In amorphous solid solutions, drug and carrier are totally miscible and soluble, originating a homogeneous molecular interaction between them [2]. In these systems, the drug and carrier interaction energy is extremely high, resulting in a really true solution. The use of polymers in the preparation of a true solid solution creates an amorphous product in which the crystalline drug is dissolved [42]. This type of amorphous solid dispersion is homogeneous on a molecular level. Therefore, only one phase is present [2]. Amorphous solid suspensions occur when the drug has limited carrier solubility or an extremely high melting point [43]. Molecularly, the obtained dispersion does not have a homogeneous structure, but is composed of two phases. Small drug particles, when dispersed in polymeric carriers, are able to provide an amorphous final product. When a drug is both dissolved and suspended in the carrier, a heterogeneous structure is obtained with mixed properties of amorphous solid solutions and amorphous solid suspensions [2, 20]. In second generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in the carrier [40]. These systems are able to reduce the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water soluble carrier, to provide better

wettability and dispersibility of the drug by the carrier material, and to produce amorphous forms of the drug and carriers [44, 45]. In these solid dispersions, the carrier dissolution (or mixtures of carriers) dictates the drug release profile.

Third generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The use of surfactants such as inulin [2], inutec SP1 [42], compritol 888 ATO [46], gelucire 44/14 [48] and poloxamer-407 [47] as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability. The association of amorphous polymers and surfactants has also been reported. For instance, the dissolution rate and bioavailability of LAB68, a poor water soluble drug, were improved after being dispersed in a mixture of PEG and polysorbate 80. The bioavailability of this solid dispersion was 10-fold higher compared to the dry blend of micronized drug. In addition, the solid dispersion system was physically and chemically stable for at least 16 months [49]. HPMC was also associated with poloxamer and polyoxyethylene hydrogenated castor oil to prepare an amorphous felodipine solid dispersion [36]. The inclusion of surfactants in the formulation containing a polymeric carrier may help to prevent precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles [6].

The advantageous properties of solid dispersions

Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h}$$

crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability [59].

Particles with reduced particle size and increased dissolution rate

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. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability [60].

The fact that more than 40% of newly discovered drugs have little or negligible water solubility presents a serious challenge to the successful development and commercialization of new drugs in the pharmaceutical industry (Connors & Elder, 2004). Solubility and permeability are the main factors that control oral bioavailability of a drug substance. Generally, when the drug solubility in water is less than 10 mg/ml, dissolution is the rate-limiting step in the process of drug absorption (Habib, 2000). Factors influencing drug dissolution rate in aqueous solution are described in Noyes-Whitney equation:

where dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the drug, C_s is the solubility of the drug in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving drug (Leuner & Dressman, 2000). According to this equation, dissolution rate can be increased through increasing the surface area, and this can be achieved through reducing the particle size.

Different methods have been used to reduce the particle size, such as micronization, recrystallization, freeze drying and spray drying. Micronization of poorly soluble drugs by milling has been used for many years in the pharmaceutical industry in order to enhance the dissolution rate of those drugs. For example the dissolution rate of micronized spironolactone was higher than that of the standard form (McInnes *et al.*, 1982). However, fine particles may not always produce the expected faster dissolution. This primarily results from the aggregation and agglomeration of fine particles. In addition, poor wettability of fine powders may reduce the dissolution rate (Bloch & Speiser, 1987; Rippie, 1986). Solid dispersion techniques have been used to enhance the dissolution rate of many poorly water soluble drugs. Particle size reduction and reduced agglomeration would both increase the exposed surface area of the drug. When solid solutions or amorphous precipitations are formed, particle size of the active ingredient is reduced to the minimum level. In addition, the carrier material may contribute to increasing the dissolution rate through its solubilizing and wettability-enhancing properties. It was reported that urea increased the dissolution rate of chlorpropamide incorporated into

urea, through its solubilizing properties (Ford & Rubenstein, 1977). The enhancement in dissolution rate as a result of solid dispersion formation, relative to pure drug, varies from as high as 400-fold to less than two-fold (Vadnere, 2002).

Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions [52]. It was observed that even carriers without any surface activity, such as urea [18] improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects [61]. Recently, the inclusion of surfactants [42, 62] in the third generation solid dispersions reinforced the importance of this property.

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 [59, 63].

Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility [29, 29]. 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 [64]. 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 [53]. 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 [62].

Strategies to avoid drug recrystallization

Recrystallization is the major disadvantage of solid dispersions. As amorphous systems, they are thermodynamically unstable and have the tendency to change to a more stable state under recrystallization. Molecular mobility is a key factor governing the

stability of amorphous phases, because even at very high viscosity, below the glass transition temperature (T_g), there is enough mobility for an amorphous system to crystallize over pharmaceutically relevant time scales. Furthermore, it was postulated that crystallization above T_g would be governed by the configurational entropy, because this was a measure of the probability of molecules being in the appropriate conformation, and by the mobility, because this was related to the number of collisions per unit time [67, 68]. Several experiments have been conducted to understand the stabilization of solid dispersions. Recent studies observed very small reorientation motions in solid dispersions showing a detailed heterogeneity of solid dispersions and detecting the sub-glass transition beta-relaxation as well as alpha-relaxation [69], which may lead to nucleation and crystal growth [66]. Molecular mobility of the amorphous system depends, not only on its composition, but also on the manufacturing process as stated by Bhugra *et al.* [70]. Solid

dispersions exhibiting high conformational entropy and lower molecular mobility are more physically stable [67]. Polymers improve the physical stability of amorphous drugs in solid dispersions by increasing the T_g of the miscible mixture, thereby reducing the molecular mobility at regular storage temperatures, or by interacting specifically with functional groups of the drugs. For a polymer to be effective in preventing crystallization, it has to be molecularly miscible with the drug [56, 71]. For complete miscibility, interactions between the two components are required. It is recognized that the majority of drugs contain hydrogen-bonding sites, consequently, several studies have shown the formation of ion-dipole interactions and intermolecular hydrogen bonding between drugs and polymers, and the disruption of the hydrogen bonding pattern characteristic to the drug crystalline structure. These lead to a higher miscibility and physical stability of the solid dispersions. Specific drug polymer interactions were observed by Teberkidis *et al.*, showing that interaction energies, electron density, and vibrational data revealed a stronger hydrogen bond of felodipine with PVP than with PEG, which was in agreement with the dissolution rates of the corresponding solid dispersions. [71-74]

Advantages of solid dispersions over other strategies to improve bioavailability of poorly water soluble drugs

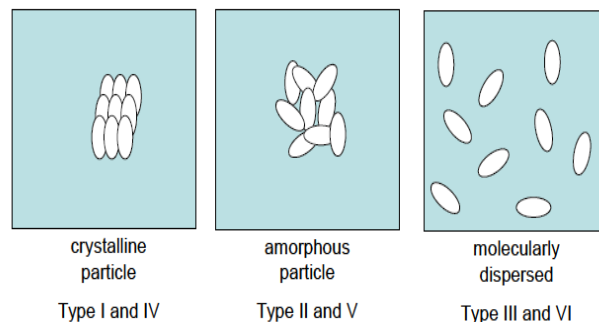
Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches. Chemical approaches to improving bioavailability without changing the active target can

be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Furthermore, it is common that salt formation does not achieve better bioavailability because of its *in-vivo* conversion into acidic or basic forms [51, 52]. Moreover, these types of approaches have the major disadvantage that the sponsoring company is obliged to perform clinical trials on these forms, since the product represents a NCE [2]. Formulation approaches include solubilization and particle size reduction techniques, and solid dispersions, among others. Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do. Milling or micronization for particle size reduction is commonly performed as approaches to improve solubility, on the basis of the increase in surface area. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 μ m which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine and, consequently, to improve the bioavailability. Moreover, solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle. [51-55]

Solid dispersions disadvantages

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization [47, 56]. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization [57]. Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate [58]. Therefore, exploitation of the full potential of amorphous solids requires their stabilization in solid state, as well as during *in-vivo* performance [27].

The limitations of this technology have been a drawback for the commercialization of solid



dispersions. The limitations include

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

Detection of crystallinity in solid dispersions [75]

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions (Figure.3). Many attempts have been made to investigate the molecular arrangement in solid dispersions. However, most effort has been put in discrimination between amorphous and crystalline material. Consequently, 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. 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, e.g. solid dispersions of type II or III and V or VI (see previous section).

Fig. 4: Schematic representation of three modes of incorporation of the drug in a solid dispersion

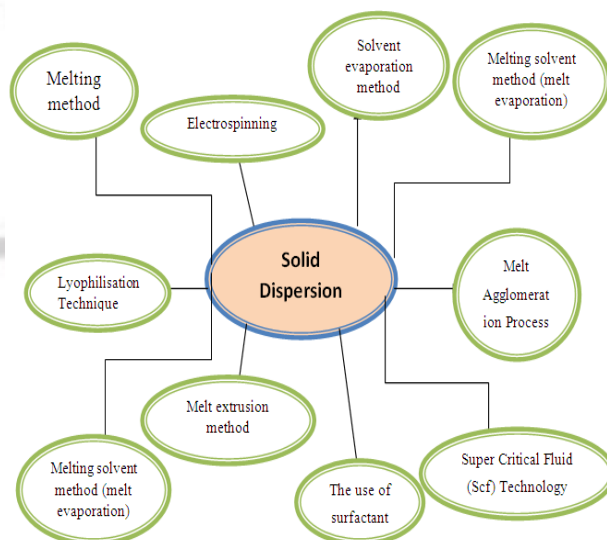
Currently, the following techniques are available to detect (the degree of) crystallinity:

- 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.
- 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 [52]. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99% in pure material. However in solid dispersions only qualitative detection was possible.

- Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples. In some studies, amorphous materials were plasticized by water sorption and crystallized during the experiment. However, crystallization can be accompanied by expel of water depending on the degree of hydration of crystalline material. In this case, the loss of water is used to calculate the amount of amorphous material. However, water vapour sorption in a binary mixture, e.g. solid dispersions, can be much more complicated than in pure materials, firstly because water vapour sorption is not always proportional to the composition of a binary intimately mixed system. The second complication is that matrix or drug crystallization during water vapour sorption is often not complete within the experimental time scale due to sterical hindrance and proceeds to an unknown extent.
- Isothermal Microcalorimetry measures the crystallization energy of amorphous material that is heated above its T_g. 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.
- Dissolution Calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic. The dissolution energies of the two components in both crystalline and amorphous state should be determined in separate experiments in order to use this technique quantitatively. However, also drug-matrix interactions will contribute to the dissolution energy of the solid dispersion.
- 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.

- The extent of supersaturation during dissolution experiments of solid dispersions are sometimes correlated to the mode of incorporation of the drug. It is unmistakable that the mode of incorporation largely determines the dissolution behaviour, but knowledge about dissolution behaviour is too poor to draw any conclusions from dissolution experiments, because it cannot be excluded that during dissolution crystallization of the drug occurs.

Methods of preparation of solid dispersions

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

- 1 Melting method
- 2 Solvent method
- 3 Melting solvent method (melt evaporation)
- 4 Melt extrusion methods
- 5 Lyophilization techniques
- 6 Melt agglomeration Process
- 7 The use of surfactant
- 8 Electrospinning
- 9 Super Critical Fluid (Scf) technology

Fig. 5: Methods of preparation of solid dispersion

1. Melting method

The melting or fusion method is the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures [76].

However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

2. Solvent method

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents [77].

However, some disadvantages are associated with this method such as

- 1) The higher cost of preparation.
- 2) The difficulty in completely removing liquid solvent.
- 3) The possible adverse effect of traces of the solvent on the chemical stability
- 4) The selection of a common volatile solvent.
- 5) The difficulty of reproducing crystal form.
- 6) In addition, a super saturation of the solute in the solid system cannot be attained except in a System showing highly viscous properties.

3. Melting solvent method (melt evaporation)

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of

polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg [76].

4. Melt extrusion method

The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed [78].

Solid dispersion by this method is composed of active ingredient and carrier, and prepared by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w) [79]. The screw-configuration consists of two mixing zones and three transport zones distributed over the entire barrel length, the feeding rate is fixed at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185°C from feeder to die. The extrudates are collected after cooling at ambient temperature on a conveyor belt. Samples are milled for 1 min with a laboratory-cutting mill and sieve to exclude particles >355µm [80].

5. Lyophilization Technique

Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of as a molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion [81].

6. Melt Agglomeration Process

This technique has been used to prepare solid dispersion wherein the binder acts as a carrier. In addition, solid dispersion are prepared either by heating binder, drug and excipient 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 excipient (spray-on procedure) by using a high shear mixer [83]. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersion by melt agglomeration. It has been found that the melt in procedure gives a higher dissolution rates than the spray-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 homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles [84].

7. Melt Agglomeration Process

The utility of the surfactant systems in solubilization is very important. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions [85-86].

8. Electrospinning

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle [87]. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor's cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The

Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited

If the viscosity increases, the charged jet is dried [88]. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future [89].

9. Super Critical Fluid (Sef) Technology

The supercritical fluid antisolvent techniques, carbon dioxide are used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system, precipitation with a compressed fluid antisolvent, gas anti-solvent, solution enhanced dispersion by supercritical fluids, and supercritical antisolvent. The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently [90]. Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component) [91].

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 [92].

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 [93].

Water vapour sorption

Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different [94]. 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) [95]. 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 [96]. 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) [97]. 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 than 10% was indicative of homogeneous distribution. Because of the pixel size of 2 μm^3 , 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 [98]. Therefore this technique can be used to assess the amount of molecularly dispersed drug [99]. And from that the fraction of drug that is dispersed as separate molecules is calculated [100].

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.

References

1. Noyes, A.A., and Whitney W.R., (1897). The rate of solution of solid substances in their own solutions, *J. Am. Chem. Soc.*, 19: 930-934.
2. Van Drooge, D.J. et al. (2006). Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. *Int. J. Pharm.*, 310: 220-229.
3. Galia, E., Nicolaides, E., Hoërter, D., LoÈbenberg, R., Reppas, C., and Dressman, J.B., (1998). Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. *Pharm. Res.*, 15: 698-705.
4. Sengodan guruswamy, V., and Mishra, D.N., 2006. Preparation and evaluation of solid dispersion of meloxicam with skimmed milk. *The Pharmaceutic. Soc. Jap.*, 126(2): 93-97.
5. Hancock, B.C., and Zogra, G., (1997). Characteristics and significance of the amorphous state in pharmaceutical systems (review). *J. Pharm. Sci.*, 86: 1-12.
6. Hoerter, D., and Dressman, J.B., (1997). Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract (review). *Adv. Drug Delivery Rev.*, 25-14.
7. Loftsson, T., and Brewster, M.E., (1996). Pharmaceutical application of cyclodextrins. 1. Drug solubilisation and stabilization (review). *J. Pharm. Sci.*, 85: 1010-1025.
8. Sekiguchi, K., and Obi, N., (1961). Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chem. Pharm. Bull.*, 9: 866-872.
9. Taylor, L.S., and Zogra, G., (1997). Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.*, 14: 1691-1698.
10. Goldberg, A.H., Gibaldi, M., and Kanig, J.L., (1966). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II \pm experimental evaluation of a eutectic mixture: urea \pm acetaminophen system. *J. Pharm. Sci.*, 55: 482-487.
11. Chiou, W.L., and Rielman, S., (1971). Pharmaceutical application of solid dispersion system. *J. Pharm. Sci.*, 60: 1281-1302.
12. Goldberg, A.H., Gibaldi, M., and Kanig, J.L., (1965). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures I theoretical considerations and discussion of the literature. *J. Pharm. Sci.*, 54: 1145-1148.
13. Kreuter, J., Kreuter, J., and Herzfeldt, C.D., (1999). *Grundlagen der Arznei-formenlehre Galenik*, 2, Springer, Frankfurt am Main. 262-274.
14. Chiou, W.L., and Riegelman, S., (1969). Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.*, 58: 1505-1510.
15. Vasconcelos, T.F., Sarmento, B., and Costa, P., (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug discovery today*, 12: 1069-1070.
16. Sekiguchi, K., and Obi, N., (1964). Studies on Absorption of Eutectic Mixture. II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. *Chem. Pharm. Bull.*, 12: 134-144
17. Sekiguchi, K. and Obi, N., (1961) Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chem. Pharm. Bull.*, 9: 866-872.
18. Levy, G., (1963). Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. *Am. J. Pharm. Sci.*, 135: 78-92.

19. Kaning, J.L., (1964). Properties of Fused Mannitol in Compressed Tablets. *J. Pharm. Sci.*, 53: 188–192.
20. Goldberg, A.H., et al. (1966). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. IV. Chloramphenicol– urea system. *J. Pharm. Sci.*, 55: 581–583.
21. Simonelli, A.P., et al. (1969). Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. *J. Pharm. Sci.*, 58: 538–549.
22. Chiou, W.L., and Riegelman, S., (1969). Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.*, 58: 1505–1510.
23. Urbanetz, N.A., (2006). Stabilization of solid dispersions of nimodipine and polyethylene glycol 2000. *Eur. J. Pharm. Sci.*, 28: 67–76.
24. Vilhelmsen, T., et al. (2005). Effect of a melt agglomeration process on agglomerates containing solid dispersions. *Int. J. Pharm.*, 303: 132–142.
25. Karavas, E., et al. (2006). Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics. *Eur. J. Pharm. Biopharm.*, 64: 115–126.
26. Drooge, J.V., et al. (2006). Characterization of the Mode of Incorporation of Lipophilic Compounds in Solid Dispersions at the Nanoscale Using Fluorescence Resonance Energy Transfer (FRET). *Macromol. Rapid Commun.*, 27: 1149–1155.
27. Pokharkar, V.B., et al. (2006). Development, characterization and stabilization of amorphous form of a low Tg drug. *Powder Technol.*, 167: 20–25.
28. Hasegawa, S., et al. (2005). Effects of water content in physical mixture and heating temperature on crystallinity of troglitazone-PVP K30 solid dispersions prepared by closed melting method. *Int. J. Pharm.*, 302: 103–112.
29. Lloyd, G.R., et al. (1999). A calorimetric investigation into the interaction between paracetamol and polyethylene glycol 4000 in physical mixes and solid dispersions. *Eur. J. Pharm. Biopharm.*, 48: 59–65.
30. Yoshihashi, Y., et al. (2006). Estimation of physical stability of amorphous solid dispersion using differential scanning calorimetry. *J. Therm. Anal. Calorim.*, 85: 689–692.
31. Guyot, M., et al. (1995). Physicochemical characterization and dissolution of norfloxacin/cyclodextrin inclusion compounds and PEG solid dispersions. *Int. J. Pharm.*, 123: 53–63.
32. Yao, W.W., et al. (2005). Thermodynamic properties for the system of silybin and poly(ethylene glycol) 6000. *Thermochim. Acta.*, 437: 17–20.
33. Chiou, W.L., and Riegelman, S., (1970). Oral absorption of griseofulvin in dogs: increased absorption via solid dispersion in polyethylene glycol 6000. *J. Pharm. Sci.*, 59: 937–942.
34. Ceballos, A., et al. (2005). Influence of formulation and process variables on in vitro release of theophylline from directly-compressed Eudragit matrix tablets. *Fairmaco.*, 60: 913–918.
35. Huang, J., et al. (2006). Nifedipine solid dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blend for controlled drug delivery: Effect of drug loading on release kinetics. *Int. J. Pharm.*, 319: 44–54.
36. Won, D.H., et al. (2005). Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. *Int. J. Pharm.*, 301: 199–208.
37. Konno, H., and Taylor, L.S., (2006). Influence of different polymers on the crystallization tendency of molecularly dispersed amorphous felodipine. *J. Pharm. Sci.*, 95: 2692–2705.
38. Verreck, G., et al. (2006). Hot stage extrusion of p-amino salicylic acid with EC using CO₂ as a temporary plasticizer. *Int. J. Pharm.*, 327: 45–50.
39. Tanaka, N., et al. (2005). Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine. *J. Contr. Release.*, 108: 386–395.
40. Rodier, E., et al. (2005). A three step supercritical process to improve the dissolution rate of Eflucimibe. *Eur. J. Pharm. Sci.*, 26: 184–193.
41. Garcia-Zubiri, I.X., et al. (2006). Thermal stability of solid dispersions of naphthalene derivatives with [beta]-cyclodextrin and [beta]-cyclodextrin polymers. *Thermochim. Acta.*, 444: 57–64.
42. Vanden Mooter, G., et al. (2006). Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs. *Int. J. Pharm.*, 316: 1–6.
43. Chiou, W.L., and Riegelman, S., (1971). Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.*, 60: 1281–1302.
44. Karata, A., et al. (2005). Improved solubility and dissolution rate of piroxicam using gelucire 44/14 and labrasol. *Farmaco.*, 60: 777–782.

45. Damian, F., et al. (2000). Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14. *Eur. J. Pharm. Sci.*, 10: 311–322.
46. Li, F.Q., et al. (2006). In vitro controlled release of sodium ferulate from Compritol 888 ATO-based matrix tablets. *Int. J. Pharm.*, 324: 152–157.
47. Chauhan, B., et al. (2005). Preparation and evaluation of glibenclamidepolyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. *Eur. J. Pharm. Sci.*, 26: 219–230.
48. Yuksel, N., et al. (2003). Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: in vitro and in vivo evaluation. *Eur. J. Pharm. Biopharm.*, 56: 453–459.
49. Dannenfelser, R.M., et al. (2004). Development of clinical dosage forms for a poorly water soluble drug I: Application of polyethylene glycol-polysorbate 80 solid dispersion carrier system. *J. Pharm. Sci.*, 93: 1165–1175.
50. Cutler, L., et al. (2006). Development of a P-glycoprotein knockout model in rodents to define species differences in its functional effect at the blood-brain barrier. *J. Pharm. Sci.*, 95: 1944–1953.
51. Serajuddin, A.T., (1999). Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.*, 88: 1058–1066.
52. Karavas, E., et al. (2006). Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. *Eur. J. Pharm. Biopharm.*, 63: 103–114.
53. Craig, D.Q.M., (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm.*, 231: 131–144.
54. Muhrer, G., et al. (2006). Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: Generation of drug microparticles and drug-polymer solid dispersions. *Int. J. Pharm.*, 308: 69–83.
55. Rasenack, N., and Muller, B.W., (2004). Micron-size drug particles: common and novel micronization techniques. *Pharm. Dev. Technol.*, 9: 1–13.
56. Vasanthavada, M., et al. (2004). Phase behavior of amorphous molecular dispersions I: Determination of the degree and mechanism of solid solubility. *Pharm. Res.*, 21: 1598–1606.
57. Johari, G.P., et al. (2005). Dielectric studies of molecular motions in amorphous solid and ultraviscous acetaminophen. *J. Pharm. Sci.*, 94: 2207–2223.
58. Wang, X., et al. (2005). Solid state characteristics of ternary solid dispersions composed of PVP VA64, Myrj 52 and itraconazole. *Int. J. Pharm.*, 303: 54–61.
59. Ghaderi, R., et al. (1999). Preparation of biodegradable microparticles using solution enhanced dispersion by supercritical fluids (SEDS). *Pharm. Res.*, 16: 676–681.
60. Bikiaris, D., et al. (2005). Physicochemical studies on solid dispersions of poorly water-soluble drugs: Evaluation of capabilities and limitations of thermal analysis techniques. *Thermochim. Acta.*, 439: 58–67.
61. Kang, B.K., et al. (2004). Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *Int. J. Pharm.*, 274: 65–73.
62. Ghebremeskel, A.N., et al. (2007). Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer-surfactant combinations using solubility parameters and testing the processability. *Int. J. Pharm.*, 328: 119–120.
63. Vasconcelos, T., and Costa, P., (2007). Development of a rapid dissolving ibuprofen solid dispersion. In *PSWC – Pharmaceutical Sciences World Conference.*, 23:11-130.
64. Taylor, L.S., and Zografi, G., (1997). Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.*, 14: 1691–1698.
65. Zhou, D., et al. (2007). A calorimetric investigation of thermodynamic and molecular mobility contributions to the physical stability of two pharmaceutical glasses. *J. Pharm. Sci.*, 96: 71–83.
66. Yoshioka, M., et al. (1994). Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. *J. Pharm. Sci.*, 83: 1700–1705.
67. Zhou, D., et al. (2002). Physical stability of amorphous pharmaceuticals: Importance of configurational thermodynamic quantities and molecular mobility. *J. Pharm. Sci.*, 91: 1863–1872.
68. Shmeis, R.A., et al. (2004). A mechanistic investigation of an amorphous pharmaceutical and its solid dispersions, part I: a comparative analysis by thermally stimulated depolarization current and differential scanning calorimetry. *Pharm. Res.*, 21: 2025–2030.

69. Bhugra, C., et al. (2007). Prediction of the onset of crystallization of amorphous sucrose below the calorimetric glass transition temperature from correlations with mobility. *J. Pharm. Sci.*, 96: 1258–1269.
70. Vasanthavada, M. et al. (2005) Phase behavior of amorphous molecular dispersions II: Role of hydrogen bonding in solid solubility and phase separation kinetics. *Pharm. Res.*, 22: 440–448.
71. Schachter, D.M. et al. (2004) Solid state NMR perspective of drug-polymer solid solutions: a model system based on poly(ethylene oxide). *Int. J. Pharm.*, 281: 89–101.
72. Teberekidis, V.I. and Sigalas, M.P. (2006) Theoretical study of hydrogen bond interactions of felodipine with polyvinylpyrrolidone and polyethyleneglycol. *THEOCHEM.*, 803: 29–38.
73. Vanden Mooter, G., et al. (2001). Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *Eur. J. Pharm. Sci.* 12, 261–269. foaming agent on the hot stage extrusion of itraconazole with EC 20 cps. *J. Supercrit. Fluids.*, 40: 153–162.
74. Dissertations.ub.rug.nl/FILES/faculties/science/2006/d.j./c1.pdf
75. Corrigan, O.I., and Healy, A.M., (2002). Surface active carriers in pharmaceutical products and system: in “*Encyclopedia of pharmaceutical technology*”, New York, 2nd edition, Marcel Dekker Inc. 2639-2653.
76. Goldberg, A., Gibaldi, M., and Kanig, L., 1996. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II experimental evaluation of a eutectic mixture: urea-acetaminophen system, *J. Pharmaceut. Sci.*, 55: 482-487.
77. Serajuddin, A., 1999. Solid dispersion technique. *J. Pharmaceut. Sci.*, 88 (10): 891-900.
78. Narang, A., and Shrivastava, A., 2002. Melt extrusion solid dispersion technique. *Drug Dev. Ind. Pharm.*, 26(8): 111-115.
79. Breitenbach, J., 2002. Melt extrusion: from process to drug delivery technology. *Europ. J. Pharmaceut. Biopharmaceut.*, 54: 107-117.
80. Chokshi, R., and Hossein, Z., 2004. Hot Melt Extrusion Technique: A Review. *Int. J. Pharmaceut. Res.*, 3: 3-16.
81. Perissutti, B., Newton, J.M., Podezeck, F., and Rubessa, F., 2002. Preparation of extruded Carbamazepine and PEG 4000 as a potential rapid release dosage form. *Europ. J. Pharmaceut. Biopharmaceut.*, 53: 125-132.
82. Vilhelmsen, T., Eliassen, H., and Schaefer, T., 2005. Effect of a melt agglomeration process on agglomerates containing solid dispersions. *Int. J. Pharmaceut.*, 303 (1- 2): 132-142.
83. Tsinontides, S.C., Rajniak, P., Hunke, W.A., and Placek, J., 2004. Freeze drying-principles and practice for successful scale-up to manufacturing. *Int. J. Pharmaceut.*, 280 (1): 1-16.
84. Seo, A., and Schaefer, T., 2001. Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer. *Europ. J. Pharmaceut. Biopharmaceut.*, 52(3): 315-325.
85. Ghebremeskel, A.N., Vemavarapu, C., and Lodaya, M., 2007. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer surfactant combinations using solubility parameters and testing the processability. *Int. J. Pharmaceut.*, 308: 119-129.
86. Zhang, R., and Somasundaran, P., 2006. Advances in adsorption of surfactants and their mixtures at solid/solution interfaces. *Advances in colloid and interface science. Int. J. Pharmaceut.*, 123: 213-229.
87. Hohman, M.M, Shin, M., Rutledge, G., and Michael, P., 2001. Brenner electrospinning and electrically forced jets. II. Applications. *Phys of fluids.*, 13(8): 2221-2236.
88. Neamark, A., Rujiravanit, R., and Supaphol, P., 2006. Electrospinning of hexanoyl Chitosan. Carbohydrate polymers. *Int. J. Pharmaceut.*, 66: 298-305.
89. Zhang, W., Yan, E., Huang, Z., Wang, C., Xin, Y., Zhao, Q., and Tong, Y., 2007. Preparation and study of PPV/ PVA nanofibers via electrospinning PPV precursor alcohol solution. *Europ. Poly.*, 43: 802-897.
90. Taki, S., Badens, E., and Charbit, G., 2001. Controlled release system formed by supercritical anti-solvent coprecipitation of a herbicide and a biodegradable polymer. *J. Supercrit. Fluids.*, 21: 61-70.
91. Dohrn, R., Bertakis, E., Behrend, O., Voutsas, E., and Tassios, D., 2007. Melting point depression by using supercritical CO₂ for a novel melt dispersion micronization process. *J. Mol. Liq.*, 131-132, 53-59.
92. Kaushal, A.M, Guptam P., and Bansal, A.K., 2004. Amorphous drug delivery systems: molecular aspects, design, and performance. *Crit. Rev. Ther. Drug Carrier Syst.*, 21(3): 133-193.
93. Taylor, L.S., and Zografi, G., 1997. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharmaceut. Res.*, 14: 1691-1698.

94. Buckton, G., and Darcy, P., 1995. The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. *Int. J. Pharmaceut.*, 123: 265-271.
95. Sebhathu, T., Angberg, M., and Ahlneck, C., 1995. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. *Int. J. Pharmaceut.*, 104: 135-144.
96. Pikal, M.J., Lukes, A.L., Lang, J.E., and Gaines, K., 1978. Quantitative crystallinity determinations for beta-lactam antibiotics by solution calorimetry: correlations with stability. *J. Pharmaceut. Sci.*, 67(6): 767-73.
97. Kerc, J., and Srcic, S., 1995. Thermal analysis of glassy pharmaceuticals. *Thermochim. Acta.*, 248: 81-95.
98. Demeuter, P., Rahier, H., and Van Mele, B., 1999. The use of modulated temperature differential scanning calorimetry for the characterisation of food systems. *Int. J. Pharmaceut.*, 192(1): 77-84.
99. Cilurzo, F., Minghetti, P., Casiraghi, A., and Montanari, L., 2002. Characterization of nifedipine solid dispersions. *Int. J. Pharmaceut.*, 242(1-2): 313-317.
100. Vasanthavada, M., Tong, W.Q., Joshi, Y., and Kislalioglu, M.S., 2004. Phase behavior of amorphous molecular dispersions I: Determination of the degree and mechanism of solid solubility. *Pharmaceut. Res.*, 21(9): 1598-1606.