CHAPTER 1

INTRODUCTION
INTRODUCTION

Many compounds that are identified to have high activity during early screening have low aqueous solubility (Gibbon and Sewing, 2005). These compounds are mainly selected by high-throughput and receptor-based in vitro screening techniques. In the screening process, a certain degree of lipophilicity is often required for a drug to cross the cell membrane to reach the receptor site, and a lipophilic group is often needed for the drug to have an affinity with the receptor (Yokogawa et al., 1990; Hageluken et al., 1994; Lipinski, 2000; Lipinski et al., 2001). Unfortunately, compounds with high lipophilicity usually have low water solubility (Yalkowsky, 1999).

The therapeutic effect of drugs depends on the drug concentration at the site of action. The absorption of the drug into the systemic circulation is a prerequisite to reach the site of action for all drugs, except those drugs that are applied at the site of action, or those that are intravenously injected. After oral administration (gastro-intestinal route), many factors determine the bioavailability (fraction of drug reaching the systemic circulation). Since only dissolved drug can pass the gastro-intestinal membrane, dissolution is one of those factors. However, drug metabolism in the intestinal lumen, the intestinal wall and the liver may also reduce its bioavailability. In general it can be stated that the rate of absorption, thus the onset and extend of the clinical effect, is determined by the dissolution of the drug and the subsequent transport over the intestinal membrane and passage of the liver. These two aspects form the basis of the Biopharmaceutical Classification System (BCS), which is incorporated in the guidelines of the Food and Drug Administration (FDA) and has been discussed by Löbenberg and Amidon (Löbenberg and Amidon, 2000).

As per the Biopharmaceutical Classification System, Class-I drugs dissolve rapidly in an aqueous environment and are rapidly transported over the absorbing membrane. No strategies are required to increase their absorption. When the release of the active from the formulation is slower than the gastric emptying rate, good in vitro-in vivo correlation (IVIVC) can be expected. The absorption (rate) of class-II drugs can be enhanced by accelerating the dissolution. Class-II drugs show IVIVC as long as the in vivo dissolution rate is same as in vitro. However, because the dissolution rate is critical for class-II drugs, the in-vivo absorption can be affected by several physiological fluctuations, like the volume and pH of the intestinal juices, the presence of bile salts, food, enzymes, and bacteria, the motility of the gut and the viscosity in the gut lumen. For class-III drugs the absorption is rate limiting and in vitro dissolution experiments cannot be used to predict in vivo absorption. Also for class-IV drugs, no IVIVC can
be expected. It is up to the formulation scientist not only to increase the extent of absorption but also to improve the IVIVC. This can reduce the patient-to-patient variability and improve the bioavailability and the predictability of pharmacokinetic parameters.

It is clear that, depending on the classification of the drug, different strategies can be applied to increase or accelerate the absorption of a drug: either increasing the permeability of the absorbing membrane or increasing the amount of dissolved drug that is in contact with the absorbing membrane (Therefore, the driving force for the absorption process). Class-I drugs do not need a formulation strategy to increase the absorption. The strategy for Class-II drugs, having dissolution limitations but no permeation limitations, is to increase the amount of dissolved drug molecules at the absorption site. This has proven to be effective in many studies (Ali and Gorashi, 1884; Fawaz et al., 1996; Kai et al., 1996; El-Zein et al., 1998; Kohri, 1999). This strategy is useful as long as permeation is not limiting. The limitation depends on the transport mechanism over the membrane. When for example the drug is transported over the membrane by passive diffusion, the flux over the membrane increases proportionally with drug concentration at the absorption site. However, when drug transport is carrier mediated, this is not necessarily the case, because the transport capacity can become rate limiting. For Class-III drugs, the permeation over the membrane is rate limiting. The strategy for class-III drugs is to increase the permeability of the absorbing membrane. The strategy depends on the transport mechanism over the absorbing membrane, e.g., transcellular, paracellular or matrix mediated. Numerous studies deal with increasing membrane permeability in the gastrointestinal tract. The effect of the contents of the gut lumen or the effect of molecular properties of the drug on permeability is considered (Stenberg et al., 1999; Mineo et al., 2002). Efflux-transporters like P-glycoprotein can reduce the uptake and increase the duration of exposure to enzymatic metabolism by CYP3A4 (Watkins, 1997). Uptake-transporters like organic anion transporting polypeptide of (OATP) facilitate the drug uptake. It is found that bioflavonoids present in fruit juices inhibit the function of OATP and hence reduce the oral bioavailability of drugs (Dresser et al., 2002). However, in other studies, the intestinal CYP3A4 was inhibited by grapefruit juice resulting in increased bioavailability of midazolam, triazolam, felodipine and nifedipine (Ho, 2002). For a class-IV drug, both dissolution as well as permeability must be increased. However, increasing dissolution is more effective than increasing the permeability because in practice the amount of dissolved drug at the absorption site varies over six orders of magnitude (0.1 µg/l to 100 mg/l) whereas permeability varies over only a 50-fold range. Therefore, the potential to increase the absorption by increasing the drug concentration is
larger and it is more practical to increase the solubility even if permeability is further compromised (Curatolo et al., 1998).

In the present research work, the investigations will focus on the poorly soluble drug compounds, because, as stated above, both for class-II as well as for class-IV compounds, dissolution enhancement can significantly increase the bioavailability.

1.1. Strategies to increase the amount of dissolved drug at the absorption site

To increase the amount of dissolved drug at the absorption site several strategies can be used. The most straightforward method is to use a dosage form in which drug molecules are already dissolved in an aqueous solution. However, this may require large volumes of the liquid to dissolve the complete drug dose, which is highly unwanted. To increase the solubility buffers, surfactants or complex forming excipients like cyclodextrins can be applied. They can increase the aqueous solubility of lipophilic molecules significantly (Bayomi et al., 2002). Surfactants can form micelles entrapping hydrophobic molecules and can be used to deliver the drug in dissolved state to the gastro-intestinal tract, keeping the drug solubilized, when it is exposed to the aqueous intestinal fluids. For example, the bioavailability of a capsule in which danazol was dissolved in Tween 80 was increased 15.8 times compared to a powder filled capsule (Erlich et al., 1999). For a number of drugs, reproducible and extensive absorption after oral administration can be established by using surfactants (Pouton, 2000; Torchilin, 2001). However, their use is limited, for example when used for pulmonary administration, surfactants or most cyclodextrin-derivatives can cause irritation in the lung and are therefore, are highly undesirable (de Boer et al., 2001). Furthermore, due to the liquid state, molecular mobility is high and therefore in these formulations chemically unstable drugs are susceptible to degradation.

Another option is to dissolve the drug in an oily liquid. An example of such an application is the soft gelatine capsule that contains sesame oil in which a hydrophobic drug, i.e. Tetrahydrocannabinol (THC) is dissolved and marketed as Marinol® (Abbott Laboratories, GA, USA). However, the oil forms droplets inside the aqueous environment of the gastro-intestinal tract. The hydrophobic drug has to be transferred from the oil phase to the aqueous environment of the gastro-intestinal lumen before membrane passage can occur, a process that significantly decelerates the absorption. In vivo studies revealed that the onset of action of Marinol® capsules was very slow and that only a small amount of the drug reached the systemic blood circulation (Doyle and Spence, 1995; Grotenhermen, 2003). To solve this
problem micro-emulsions and self-emulsifying systems have been developed. Micro-emulsions are thermodynamically stable dispersions of two immiscible liquids, such as oil and water, stabilized by surfactant molecules (Constantinides, 1995). Self-emulsifying or self micro-emulsifying drug delivery systems (SEDDS) form under conditions of mild agitation very fine dispersions (<100 nm in diameter) (Pouton, 2000). SEDDS usually contain triglyceride oils and at least 25% w/w hydrophilic surfactants (HLB > 11) and 0-50% w/w hydrophilic co-solvents (Pouton, 1997; Pouton, 2000). The large surface of the oil-intestinal fluid interface provided by the small droplets guarantees a rapid and complete transfer of the lipophilic drug into the intestinal fluids. Sandimmune Neoral® is an example of a marketed product based on self-emulsification. It contains Cyclosporine A and the inter- and intra-individual variability of the pharmacokinetics has been claimed to be reduced compared to Sandimmune®, the latter forming a coarse emulsion in the gut (Kovarik et al., 1994). The fourth strategy to deal with drugs that suffer from dissolution-limited absorption is to increase their dissolution rate. Often the absorption of lipophilic drugs is decelerated by the slow rate of dissolution from the solid drug particles. Dispersion of the drug as very fine particles increases the surface area available for dissolution. According to the classical Noyes-Whitney equation this further increase the dissolution rate (Noyes, 1897). Particle size reduction may go to the nano-scale. However, even this size reduction will not lead to concentrations above the maximum solubility of the drug in the intestinal fluids.

Alternatively, solid dispersions can be used to increase the dissolution rate of poorly soluble drugs (Torrado, 1996; Kushida, 2002; Gohel and Patel, 2003), and they have proven to increase the amount of dissolved drug at the absorption site sometimes to supersaturated concentrations and consequently improve the bioavailability (Fawaz et al., 1996; Kai et al., 1996; Kohri et al., 1999). Solid dispersions have been investigated in many studies because they are highly versatile in their application. They can form the basis of products applied for various routes of administration and for various dosage forms, including the most popular dosage form, i.e., the tablet.

1.2. Solid dispersions

1.2.1. Definition of solid dispersions

The term 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 the 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 term coprecipitate (more accurately coevaporate) has also been frequently used when a solid dispersion is prepared by the solvent method, such as coprecipitates of sulfathiazole-polyvinylpyrrolidone (Simonelli et al., 1969) and reserpine-polyvinylpyrrolidone (Bates, 1969). However, the definition can now be broadened to include certain nanoparticles, microcapsules, microspheres, and other dispersions of drugs in polymers prepared by using any one of the above processes. Although most solid dispersion systems initially focused on producing increased dissolution rates. Recent attempts have been aimed at achieving other goals such as sustained release of drugs, altered solid-state properties, enhanced release of drugs from ointment & suppository bases, and improved solubility and stability.

Solid dispersion was originally used to describe the dispersion of poorly water-soluble drugs in water-soluble inert polymeric carriers. But now with advent of time and extensive research in this field, it is also used to describe the dispersion of drugs in water-insoluble polymeric carriers.

1.2.2. Classification of solid dispersions

The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished (Chiou and Riegelman, 1971). Moreover, certain combinations can be encountered, i.e., in the same sample; some molecules are present in clusters while some are molecularly dispersed. Confusingly, 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.

Solid dispersions have been classified mainly into six major categories (Chiou and Riegelman, 1971) as:

1. Simple eutectic mixtures.
2. Solid solutions.
3. Glass solutions and suspension,
4. Amorphous precipitations of a drug in a crystalline carrier, and
5. Compound or complex formations between the drug and the carrier.
6. Any combinations of these groups.
Table 1: Classification of Solid dispersion in six categories

<table>
<thead>
<tr>
<th>Solid dispersion</th>
<th>Characteristics</th>
<th>Reference in literature</th>
</tr>
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<tbody>
<tr>
<td><strong>Type</strong></td>
<td><strong>Class</strong></td>
<td><strong>Matrix</strong></td>
</tr>
<tr>
<td>I</td>
<td>Eutectic</td>
<td>Crystalline</td>
</tr>
<tr>
<td>II</td>
<td>Solid solutions</td>
<td>Continuous solid solutions</td>
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<td></td>
<td></td>
<td>Discontinuous solid solutions</td>
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<tr>
<td></td>
<td></td>
<td>Substantial solid solutions</td>
</tr>
<tr>
<td>III</td>
<td>Glass suspension</td>
<td>Amorphous</td>
</tr>
<tr>
<td></td>
<td>Glass suspension</td>
<td>Amorphous</td>
</tr>
<tr>
<td></td>
<td>Glass solution</td>
<td>Amorphous</td>
</tr>
<tr>
<td>IV</td>
<td>Amorphous precipitation in crystalline matrix</td>
<td>Crystalline</td>
</tr>
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<table>
<thead>
<tr>
<th>V</th>
<th>Complex formation</th>
<th>Can be crystalline or amorphous</th>
<th>Molecularily dispersed</th>
<th>Drug and matrix interact to form complex</th>
<th>Singh et al., 1966; Hahn and Sucker, 1989; Bayomi et al., 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI</td>
<td>Related and other designations</td>
<td>Co-precipitates</td>
<td>Mostly amorphous</td>
<td>Generally amorphous</td>
<td>Prepared by adding non-solvent to solution of drug and carrier</td>
</tr>
<tr>
<td></td>
<td>Co-evaporates</td>
<td>Can be crystalline or amorphous</td>
<td>Can be crystalline or amorphous</td>
<td>Prepared by evaporating solvent in which dispersed phase and dispersant was dissolved</td>
<td>Paradikar et al., 2004</td>
</tr>
<tr>
<td></td>
<td>Monoelectics</td>
<td>Crystalline</td>
<td>Crystalline</td>
<td>Same as eutectics, but with completely non-interacting system</td>
<td>Craig and Newton, 1991; Lloyd et al., 1997</td>
</tr>
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#### 1.2.2.1. Simple eutectic mixtures

A simple eutectic mixture consists of two compounds, which are completely miscible in the liquid state but only to a very limited extent in the solid state. Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with new composition, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug (Goldberg et al., 1966; Sekiguchi and Obi, 1971).

A eutectic mixture of a sparingly water-soluble drug and a highly water-soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline components. These components are assumed to crystallize simultaneously in very small particulate sizes. The increase in specific surface area, therefore, is mainly responsible for the increased rate of dissolution of a poorly water-soluble drug.

Differential thermal analysis (DTA) of binary mixtures normally exhibits two endotherms, but a binary mixture of eutectic composition usually exhibits a single major endotherm. In the case of a simple eutectic system, the thaw points of binary mixtures of varying compositions are equal.
to the eutectic temperature of the system. Chiou and Niazi examined griseofulvin-succinic acid solid dispersions prepared by the fusion method. They showed with the aid of x-ray diffraction and DTA, that solid solubility was negligible, contrary to earlier suggestions, and classified this system as a simple eutectic mixture (Chiou and Niazi, 1973). Additional studies of fused compositions of griseofulvin in succinic acid showed that the dissolution of griseofulvin was inversely proportional to the concentration of griseofulvin in the dispersion. This led to the conclusion that the increase in dissolution was mainly due to the decreased particle size obtained, although other factors such as increased wettability, reduction or absence of aggregation, and solubilization of the drug by the carrier at the site of the diffusion layer may have also contributed (Chiou and Niazi, 1976). On the other hand, Goldberg and coworkers obtained similar dissolution profiles for both the fused solid dispersion of acetaminophen-urea at the eutectic composition and a physical mixture of the same composition (Goldberg et al., 1966).

1.2.2. Solid Solutions
Solid solutions consist of a solid solute dissolved in a solid solvent. If the carrier is crystalline, a mixed crystal is formed because the two components crystallize together in a homogeneous one-phase system (Chiou and Riegelman, 1971). Perhaps, as suggested by Goldberg and coworkers, particle size is reduced in solid solution to molecular level, i.e., the dissolution of the drug occurs in the solid-state matrix. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems (Goldberg et al., 1966). In practice, the occurrence of solid solubility of less than 2% is considered insignificant. In binary systems, where solid solution formation is evident, the phase diagram is characterized by the disappearance of thaw points at a temperature higher than the eutectic temperature.

Chiou and Riegelman reported a marked increase in dissolution rates of the sparingly water-soluble drugs digiioxin, 17-methyl testosterone, hydrocortisone acetate, and prednisolone acetate, when dispersed in PEG 6000 (Chiou and Riegelman, 1971). This was believed to be due to the formation of colloidal or molecular dispersion of the drug in the carrier. Similarly, Goldberg and Gibaldi obtained a large increase in dissolution from the fused mixtures of chloramphenicol-urea, which formed a solid solution (Goldberg and Gibaldi, 1966).

Solid solutions can be classified according to their miscibility (continuous versus discontinuous solid solutions) or either, according to the way in which the solvate molecules are distributed in the solvendium (substitutional, interstitial or amorphous).
1.2.2.2.a Continuous and discontinuous solid solutions

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

Discontinuous solid solutions: In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Due to practical considerations, it has been suggested by Goldberg and coworker (Goldberg et al., 1965), that the term ‘solid solution’ should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component.

1.2.2.2.b Substitutional crystalline, interstitial crystalline and amorphous solid solutions

Substitutional crystalline solid solutions: Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules (Hume-Rothery and Raynor, 1954).

Interstitial crystalline solid solutions: In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is not greater than 0.59 of the solvent molecule’s molecular diameter (Reed-Hill, 1964). Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

1.2.2.3 Glass solution of suspension

The principle of glass solution formation was first reported by Chiou and Riegelman to enhance drug dissolution and absorption (Chiou and Riegelman, 1969). A glass solution is a homogeneous system in which a glassy or a vitreous form of the carrier solubilizes drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent. Glass solutions of digitoxin with PVP (Stupak and Bates, 1973), methisazone with PVP (Gidwani and Anderson, 1976), corticosteroids with dextrose or
galactose (Allen et al., 1977), sulfamethoxazole with sugars (Ghanem et al., 1980), and primidone with citric acid (Summers and Enever, 1976) have been reported.

1.2.2.4 Amorphous Precipitation

Amorphous precipitation occurs when the drug precipitates as an amorphous form in the inert carrier. The high energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.

The conversion of a drug to an amorphous form of coprecipitation resulting in increased dissolution has been reported for sulfisoxazole-PVP (Sekikawa et al., 1974a) and chloramphenicol-PVP or α-hydroxypropyl cellulose (Moriyama et al., 1978) systems. There have been other less clear examples of amorphous precipitation such as the phenytoin-PVP or sulfamethizole-PVP coprecipitate systems (Sekikawa et al., 1974b; Sekikawa et al., 1979), where the incidence of coacervation of the carrier has been believed to play a role in the particle size and solid state form of the released drug.

1.2.2.5 Compound or complex formation

This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of a drug from the complex is dependent on the solubility, dissociation constant, and the intrinsic absorption rate of the complex.

For example, PVP has been shown to retard the pharmacological actions of penicillin, novocaine, prostigmine, hexobarbital, quinine and hexylresorcinol (Chiou and Riegelman, 1971). Similarly, Geneidi and coworkers reported a decrease in dissolution rate of nitrofurantoin from its coprecipitate or physical mixture with PVP 25,000 because of the formation of an insoluble complex (Geneidi et al., 1971).

1.3 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, demixing (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 (Sekiguchi and Obi, 1961; Chiou and Riegelman, 1971). 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. Apparently, conflicting requirements should be met during the design of an adequate preparation process.

1.3.1. 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.

In the fusion method of preparation, the carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix. Several mechanisms could operate during the process of dispersion. If the drug has a high degree of solubility in the carrier, the drug could remain 'dissolved' in the solid state, yielding what is known as a solid solution. Particle size reduction under these conditions proceeds to the ultimate level leading to molecular dispersion of the drug in the carrier matrix. These systems show very high drug dissolution rates compared to control samples. If, on the other hand, the solubility of the drug in solid state is not so high, crystallites of the drug become dispersed in the matrix. Such systems show only moderate increases in dissolution rates. A third mechanism is the conversion of a drug to an amorphous form in the presence of the carrier matrix, again exhibiting different dissolution rates and solubility. Other factors that may play a role include solubilizing effect conferred by the carrier itself, improved wetting or decreased surface hydrophobicity, complexation and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties. An important limitation of the fusion method of preparation is the exposure of drugs to elevated temperatures, particularly if the carrier is a high-melting solid and the drug is heat-sensitive. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method by Sekiguchi and Obi, who used fusion method to melt a sulphathiazole-urea mixture of eutectic composition above its eutectic temperature, solidified the dispersion on an ice bath, and pulverized it to a powder. Since a supersaturation of the drug can be obtained by quenching the melt rapidly (when the solute molecules are arrested in the solvent matrix by instantaneous solidification), rapid congealing is favored (Sekiguchi and Obi, 1961). Consequently, the solidification process is often affected by stainless steel plates (Sekiguchi et al., 1964; Chiou and Riegeiman, 1969).
favor rapid heat loss. A modification of the process involves spray congealing from a modified spray drier onto cold metal surfaces, which has been used for dispersions containing mannitol (Kanig, 1964) or phenylbutazone-urea (Kreuschner et al., 1980). Spray-congealing processes are preferable since pellets of the dispersion can be produced without grinding and without altering the crystalline modification of the drug (Fromemming et al., 1978). Walker and associates demonstrated the feasibility of liquid-filling gelatin capsules with the liquid melt and avoiding grinding-induced changes in crystallinity (Walker et al., 1980).

The fusion process is technically the less difficult method of preparing dispersions, provided the drug and carrier are miscible in the molten state. Certain drug carriers, e.g., tolbutamide-mannitol display a miscibility gap within their phase diagram, and consequent irregular crystallization may lead to only moderate increases in dissolution rate and difficulties in formulation (El-Sanna et al., 1975). Kanig predicted that immiscibility and instability may occur during fusion (Kanig, 1964), and Goldberg & co-workers highlighted other potential problems such as thermal degradation, sublimation, and polymorphic transformation since metastable modifications of the drug may be formed, which convert to more stable forms during storage (Goldberg et al., 1965). Small crystallites may be obtained by quench cooling (Collett et al., 1976), but the solidification temperature will affect crystallization rates and may alter both the crystalite size and the hardness of the dispersion (Daabis et al., 1974). The solidified melt may be tacky and unhandable, and consequently novel formulation techniques are required to permit formulation into elegant dosage forms (Ford and Rubinstein, 1980; Walker et al., 1980; Ford and Rubinstein, 1981). Some dispersions e.g., griseofulvin-polyethylene glycol 6000 hardened on storage that favored pulverization, whereas others, e.g., griseofulvin-citric acid, require storage at elevated temperatures, e.g., 37°C, to facilitate hardening. However, this derivation of tacky or glassy dispersions or their comminutions may induce crystallization and modify their dissolution characteristics (Chiou, 1977). Decomposition should be avoided during fusion, but is often composition dependent (Chiou and Niazi, 1971; Ford et al., 1979) and affected by fusion time and the rate of cooling (Carcamo and Gana, 1974). Therefore, to maintain decomposition at an acceptable level, fusion may be effected at a temperature just in excess of that which completely melts both drug and carrier, though it is feasible to prepare dispersions just above the eutectic temperature when the carrier level exceeds in eutectic composition (Ford and Rubinstein, 1981).

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 (Timko and Lordi, 1984; Greenhalgh et al., 1999), which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants (Damian et al., 2002; 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 (McGinity et al., 1984; Save and Venkitachalam, 1992). 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. PEG’s melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method.

1.3.2. Hot melt extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by an extruder. When compared to melting in a vessel, the product stability and dissolution are similar (Forster et al., 2001a), 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.

![Fig. 1: Schematic of a single screw extruder (Breitenbach, 2002)](image_url)

High shear forces resulting in high local temperatures in the extruder can be a problem for heat
sensitive materials (Forster et al., 2001b; Langer et al., 2003). 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.

1.3.3. 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 (Vaugelade et al., 2001; 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 Tween 80 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. However, according to the ICH-Guidelines (CPMP/ICH/283/95, 1998), these solvents belong to Class I, comprising the most toxic solvents and should be avoided in formulation meant for oral use. 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, favouring phase separation (e.g. crystallization).

To dry the solutions, **vacuum drying** is often used (Sertsou et al., 2002; Gohel and Patel, 2003). The solution is dried by the application of vacuum and moderate heating. Sometimes, the solvent evaporation is accelerated 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) crystallizes during processing (Weuts et al., 2005).

An alternative to these drying techniques is **freeze drying**. 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 (Betageri and Makarla, 1995; Yoo et al., 2000; Sethia and Squillante, 2003). One of the reasons might be the very low freezing temperature of most organic solvents. 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 used a condenser temperature of -75°C, to dry a solution with cyclohexanol as the solvent (Betageri and Makarla, 1995). To obtain a lyophiliation process of acceptable duration, the solvent should have a sufficiently high vapour pressure. 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 results in even faster vitrification, thereby decreasing the risk for phase separation to a minimum (Costantino et al., 2002; Hu et al., 2004; Leuenberger, 2002; Rogers et al., 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).

Solid dispersion prepared by solvent removal processes was termed by Bates [Bates, 1969] as 'co-precipitates' and by others (Sekikawa et al., 1983) as 'co-evaporates'. Since larger increases in dissolution rates are generally obtained from dispersions containing the molecularly dispersed drug, the drug-to-carrier ratio is particularly important (Sekikawa et al., 1978). For instance, the acetohexamide-PVP 25,000 dispersions containing in excess of 70% polymer were amorphous and gave rapid drug release, but those containing less than 70% PVP were increasingly crystalline and gave only low dissolution rates (Sekikawa et al., 1983). Sekikawa and coworkers quantified the mechanisms of dispersion formation by solvent removal using drug-PVP models (Sekikawa et al., 1978). As evaporation proceeds, the drug concentrations reach and exceed solubility. The PVP inhibits drug crystallization, by maintaining the supersaturation, the degree of which continues to increase. If the PVP concentration is high enough to inhibit crystallization of the drug, the dispersion will appear from solution without crystallization, giving a dispersion containing amorphous drug. However, in case the PVP concentration too low, crystallization will not be inhibited and the dispersion would contain crystalline drug. Crystallization retardation is not only dependent on the drug-to-carrier ratio, but also on the physical properties of the drug molecule and the method of preparation. Sulfisoxazole-PVP dispersions of 1:3 were amorphous, but a 10:1 ratio contained crystalline drug. However, a 1:3 caffeine-PVP did not form a coprecipitate (Sekikawa et al., 1978). Amorphous hydroflumethazide-PVP systems were prepared by spray drying at lower PVP weight fractions than by other solvent removal processes and appeared to contain both amorphous hydroflumethazide and amorphous drug-PVP complexes whereas a coprecipitate did not (Corrigan et al., 1983).

1.3.4. Fusion-solvent method

In the fusion-solvent method, a carrier(s) were melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is
eliminated. Otherwise, this method faces the same criticism of solvent retention described before. This method is particularly useful for drug that have high melting points or that are thermolabile.

The feasibility of this method has been demonstrated for spironolactone and griseofulvin dispersions in PEG 6000 (Chiou and Riegelman, 1971). Other researchers have also adopted this method (Fernandez et al., 1992). Although there are advantages and disadvantages associated with this method, the choice of a method of preparation could affect the intended purpose of solid dispersion formulations. Najib and Salem have shown that ibuprofen dispersions prepared by the fusion-solvent method gave higher solubilities than those prepared by the solvent method (Najib and Salem, 1987). Similarly, higher dissolution rates were obtained for sulfamethoxazole-PEG (Singla and Vijan, 1990) or griseofulvin-PEG (Sjolkvist and Nyslrom, 1988) dispersions prepared by the fusion-solvent method as compared to coprecipitation. However, Jafari and coworkers have reported comparable results from dispersions prepared by coprecipitation and fusion-solvent methods (Jafari et al., 1988).

1.3.5. 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 (Palakodaty and York, 1999; Kompella and Koushik, 2001). When supercritical CO₂ is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO₂ is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO₂ of most pharmaceutical compounds is very low (<0.01% w/v) (Subramaniam et al., 1997) and decreases with increasing polarity (Kompella and Koushik, 2001). Therefore, scaling up this process to kilogram-scale is 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, these techniques represent alternative methods to remove solvents from a solution containing typically a drug and a polymer. Moneghini and co-workers (Moneghini et al., 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 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 (Yoo et al., 2000).

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 Anti-Solvent (SAS) when supercritical CO₂ is used, or Aerosol Solvent Extraction System (ASES), and Solution Enhanced Dispersion by Supercritical fluids (SEDS) (Subramaniam et al., 1997; Kompella and Koushik, 2001). The critical step in these precipitation techniques is 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., 2001). Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix (Sethia and Squillante, 2002).

1.3.6. Other methods

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).

In another process called supercritical fluid impregnation, 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 has been investigated for poly(methyl methacrylate) (Vincent et al., 1997) but can be applied for other polymers as well.
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 diameter can be adjusted by surface tension, electrical field and dielectric constant (Sethia and Squillante, 2003). After rapid evaporation of the solvent, the fibres can be directly used or milled and further processed (Verreck et al., 2003).

1.4. Characterization of solid dispersions

A number of methods have been used to characterize solid dispersions including:

1. Thermal methods of analysis: differential, thermal and thermomicroscopical
2. Powder x-ray diffraction;
3. Microscopical studies, including the use of polarized light and the scanning electron microscope
4. Spectroscopic methods, especially I.R
5. Dissolution rate determination
6. Thermodynamic investigations involving determinations of the heats of dissolution, and the melting points in order to calculate the resulting changes in entropy
7. Dynamic dialysis to characterize the formation of highly supersaturated solutions after dissolution of solid dispersions.

The most important and frequently used methods among these are thermoanalytical, powder x-ray diffraction and dissolution rate.

1.4.1. Thermal methods of analysis:

Differential thermal analysis (DTA) is an effective thermal method for studying the phase equilibria of pure substances or solid mixtures and the most frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC) (Kerc and Srlic, 1995). Differential heat changes that accompany physical and chemical changes are recorded as a function of temperature as the substance is heated at a uniform rate. 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.

Clearly, many techniques can distinguish between the crystalline and amorphous state for pure materials. However, in a mixture of two components, like in a solid dispersion, it is always necessary to know the interaction between the individual components and the effect thereof on the physical property that is being quantified and from which the crystallinity is to be derived.

In addition to thawing and melting, polymorphic transitions, evaporation, sublimation, desolvation, and other types of changes such as decomposition of the sample can be detected. DTA records energy changes occurring in the sample as it is being heated either exothermic or endothermic. However, for the interpretation of DTA thermograms, prior knowledge of the type of reactions that may be occurring is essential. For instance, it is necessary to know whether the sample is undergoing polymorphic change, decomposition, or desolvation. DTA has been used routinely to identify different types of solid dispersions (El-Banna et al., 1974; Rogers and Anderson, 1982). It has been shown by Borchardt and Daniels (Borchardt and Daniels, 1957) that the total heat of reaction, $\Delta H$, is proportional to the area under the DTA peak, as described by

$$\Delta H = K \int_{t_1}^{t_2} \Delta T \,dT - KA$$

![Equation 1](image)

where, $K$ is a proportionality constant, $\Delta T$ is the temperature differential, $A$ is the area under the DTA peak, $\Delta T$ is the differential time going from $t_1$ to $t_2$.

Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. In case of amorphous matrices, TMDSC has been used to discriminate between solid dispersions type V and VI (Six et al., 2004). Furthermore, the value of the $T_g$ 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 (De Meuter 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). Moreover, the fraction of drug present in amorphous state can be assessed (Guinot and Leveiller, 1999).
Thermomicroscopical analysis is a visual method of analysis using a polarized microscope with a hot state to determine the (thaw and melting points of solids. Its advantages are the small amount of sample required (virtually one crystal) and direct observation of the changes taking place in the sample through the thaw and melt stages. However, it does not provide the thermodynamics of the melting process and in some instances it is not as sensitive as DTA. The technique has been used by others often to support DTA or DSC measurements [Ford and Rubinstein, 1978; Daabis et al., 1974].

Isothermal Microcalorimetry measures the crystallization energy of amorphous material that is heated above its \( T_a \) (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.

1.4.2. Powder x-ray diffraction

X-rays have been used in crystal structure studies in two different ways, that is single crystal X-ray crystallography dealing with the determination of bond angles and interatomic distances, and powder x-ray diffraction dealing with the study of crystal lattice parameters, where the x-ray diffraction intensity from a sample is measured as a function of the diffraction angles. Thus, changes in the diffraction pattern indicate changes in crystal structure. The relationship between the wavelength, \( \lambda \), of the x-ray, the angle of diffraction, \( \theta \), and the distance between each set of atomic planes of crystal lattice, \( d \), is given by Bragg's equation:

\[
M\lambda = 2d\sin\theta
\] ........................ [Eqn. 2]

Where, 'M' represents the order of diffraction; \( \lambda \) = wavelength of x-ray; \( d \) = length of the slit of diffractometer; and \( \theta \) = angle of diffraction.

X-ray diffraction spectra of simple eutectic systems show peaks of each crystalline component. Any change in the crystal lattice parameter displaces the diffraction peaks. Solids solutions exhibit a gradual shift in the positions of the diffraction lines with changes in composition. The lattice parameters of complexes are markedly different from those of pure components. Hence, the x-ray diffraction method can also be used in detecting complex formation. However, its major drawback had been the inability to differentiate between amorphous precipitation and molecular dispersion of the lattice parameter. This technique had been most frequently used by researchers to characterize solid dispersions (Chiou, 1977; McGinity et al., 1984).
1.4.3. Macroscopic techniques

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.

1.4.4. Spectroscopical method

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 (Taylor and Zografi, 1998). However in solid dispersions only qualitative detection was possible (Broman et al., 2001). 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; Rogers et al., 2002).

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 μm², uncertainty remains about the presence of nano-sized amorphous drug particles.

1.4.5. Thermodynamic investigations

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. The dissolution energies of the two components in both crystalline and amorphous state should be determined in separate experiments in order to use this technique quantitatively. However, drug-matrix interactions also contribute to the dissolution energy of the solid dispersion.

The extent of supersaturation during dissolution experiments of solid dispersions are sometimes correlated to the mode of incorporation of the drug (Mosharraf et al., 1999). 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.
1.4.6 Other method

**Water vapour sorption** can be used to discriminate between amorphous and crystalline material when, hygroscopicity is different (Buckton and Darcy, 1995). 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 (Burnett et al., 2004). 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 (Crowley and Zografi, 2002). 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 (Wang, 2000) and proceeds to an unknown extent.

1.5. Dissolution of solid dispersions

The dissolution of a drug from a solid dispersion system consists of three processes:

1. the coprecipitate interacts with water in its vicinity,
2. finely dispersed drug in the matrix is released, and
3. solubilized drug is supersaturated in the diffusion layer.

Some of the most common reasons for increased dissolution rates from solid dispersions have been the formation of solid solution, eutectics, conversion to an amorphous form, solubilization effect by the carrier, or increased hydrophilicity of the drug due to coating by polymers.

According to the film theory of dissolution, factors affecting the rate of dissolution include the diffusion coefficient, the thickness of diffusion layer, the surface area, and the difference between the saturation concentration in the diffusion layer and the concentration of bulk solution.

A description commonly used to explain the dissolution of a solid, was originally developed by Noyes and Whitney (Noyes and Whitney, 1897). The dissolution rate of a solid can be given by:

\[
\frac{dm}{dt} = A \frac{D}{\delta} (C_s - C_{\text{sat}}) 
\]

Where, \( \frac{dm}{dt} \) is the dissolution rate (kg/s), \( A \) is surface area of solid under diffusion, \( D \) is
The diffusivity constant of the dissolving compound, $\delta$ is thickness of diffusion layer, $C_s$ is concentration of drug in solvate and $C_{bulk}$ is concentration of drug in dissolution media.

**Fig. 2:** Schematic representation of dissolution of solid

It was claimed that the dissolution rate was proportional to the difference between bulk concentration and concentration at the dissolving interface. In fact, all five parameters at the right-hand side of the equation no. 3 can be affected in order to accelerate the dissolution rate. Nernst and Brunner were the first to propose the diffusion layer model (Nernst and Brunner, 1904). They assumed that dissolution at the solid-liquid interface is rapid and transport of the solute to the bulk is completely determined by diffusion through a stagnant boundary layer surrounding the dissolving interface. A high diffusivity of the dissolving compound, $D$, establishes fast transport through the stagnant layer. Micronization of drug particles increases the surface area and has been shown to accelerate dissolution (Rasenack, 2003). Therefore, the drug in solid dispersions should be dispersed in particles as small as possible, preferably mono-molecularly. Moreover, the large surface area of the drug during dissolution of a solid dispersion can be maintained by matrices since they prevent agglomeration of small drug particles (Chiou and Riegelman, 1971). An increase in drug solubility ($C_s$) accelerates the dissolution. Solubilizers like cyclodextrins or surfactants are added to solid dispersions for this purpose. Furthermore it is known that amorphous material has a higher solubility than a crystalline material (Hancock and Zografi, 1997). The higher solubility of amorphous drugs can be expected based on thermodynamical considerations and was confirmed with experiments (Pikal et al., 1971; Corrigan et al., 1984; Hancock and Parks, 2002). For example, amorphous novobiocin showed a 10 times higher equilibrium solubility compared to the crystalline form (Mullins and Macek, 1960). $C_{bulk}$ is the concentration in the bulk and can be lowered in-vitro by increasing the dissolution volume and in-vivo by increasing the permeation rate over the intestinal membrane and inhibiting p-glycoprotein-like transporters.
1.6. Physical stability of amorphous solid dispersions

Amorphous materials are thermodynamically unstable and will have a natural tendency to crystallize, because the crystalline state has a lower energy compared to amorphous material. However, amorphous material can be kinetically stable, which implies that the equilibrium state, i.e., crystalline, is not reached within the timeframe of the experiment or shelf life of the product. The dissolution behaviour of solid dispersions must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure. For optimal stability of amorphous solid dispersions, the molecular mobility should be as low as possible. However, solid dispersions, partially or fully amorphous, are thermodynamically unstable. In solid dispersions containing crystalline particles (type IV), these particles form nuclei that can be the starting point for further crystallization. It has been shown that such solid dispersions show progressively poorer dissolution behaviour during storage (Weuts et al. 2005). In solid dispersions containing amorphous drug particles (type II and V) the drug can crystallize, but a nucleation step is required prior to that. In homogeneous solid dispersions (type III and VI) the drug is molecularly dispersed, and crystallization requires another step. Before nucleation can occur, drug molecules have to migrate through the matrix. Therefore, physical degradation is determined by both diffusion and crystallization of drug molecules in the matrix. It should be noted that in this respect it is better to have a crystalline matrix, because diffusion in such a matrix is much slower. Physical changes are depicted in fig. 3.

![Diagram showing physical changes in solid dispersion resulting in crystallization](image)

**Fig. 3:** Physical changes in solid dispersion resulting in crystallization

The physical stability of amorphous solid dispersions should be related not only to crystallization of drug, but also to any change in molecular structure including the distribution of the drug. Moreover, the physical state of the matrix should be monitored, because changes therein are likely to alter the physical state of the drug and drug release as well.