Chapter 1
Introduction: Production, stability, and dissolution of solid dispersions to improve the bioavailability of class II lipophilic drugs

1.1. Contents chapter 1

1.2. Improving therapeutic effect of class-II drugs.

1.2.1. Factors affecting systemic absorption

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, ergo 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 discussed by Löbenberg and Amidon [1]. According to the BCS, four different types of drug absorption regimes are distinguished. They are explained in Table 1.

Table 1: Biopharmaceutical Classification System according to [1]

Class	Dissolution in aqueous environment	Permeation over (intestinal) membrane
I	Fast	Fast
II	Slow	Fast
III	Fast	Slow
IV	Slow	Slow

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 to increase the extent of absorption but also to improve the IVIVC. This will 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 (ergo 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 [2-6]. 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 gastro-intestinal tract. The effect of the contents of the gut lumen or the effect of molecular properties of the drug on permeability are considered [7, 8]. Efflux-transporters like P-glycoprotein can reduce the uptake and increase the duration of exposure to enzymatic metabolism by CYP3A4 [9]. Uptake-transporters like organic anion transporting polypeptide (OATP) facilitate the drug uptake. It is found that bioflavonoids present in fruit juices inhibit the function OATP and hence reduce the oral bioavailability of drugs [10]. However, in other studies, the intestinal CYP3A4 was inhibited by grapefruit juice resulting in increased bioavailability of midazolam, triazolam, felodipine and nifedipine [11].

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 [12].

Let it be noted that the classification system intends to differentiate orally administered drugs but it can be applied more generally to absorption after administration via other routes too. For example, to obtain systemic absorption using pulmonary administration, the drug has to dissolve in the mucus of the alveoli before it can be transported over the alveolar membrane.

Absorption problems can be predicted according to Lipinski´s rule of five [13].

Lipinski's rule of 5 learns that poor absorption and permeation is likely when:
- More than 5 H-bond donors (expressed as the sum of OH's and NH's) - More than 10 H-bond acceptors (expressed as the sum of N's and O's) - The molecular weight is more than 500(g/mole) - The log P (log of ratio of solubilities in octanol/water) is larger than 5

Molecules that evolve of the high throughput screening methods intended to identify new potential drug candidates tend to be more and more lipophilic [13]. Mostly, they are class-II drugs and their oral bioavailability is dissolution rate limited. More generally, absorption into the systemic blood circulation by dermal, pulmonal, nasal, sublingual, or gastro-intestinal administration always involves transport of separate (dissolved) drug molecules through an absorbing membrane (figure 1). Also for most local treatments a therapeutic effect is only obtained when the drug is in the dissolved state. For example, for local pulmonary treatment, the drug should dissolve in the mucus to give a local effect.

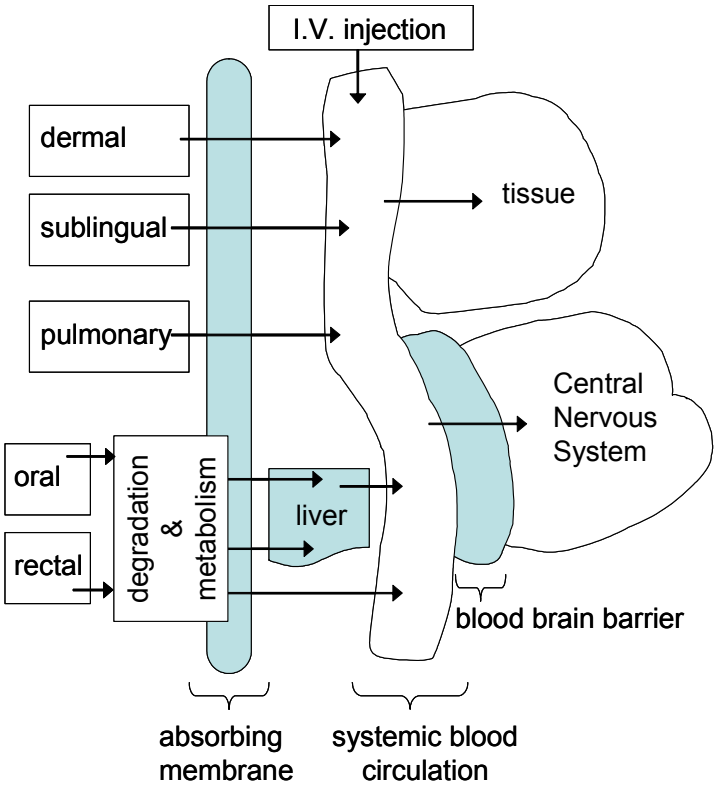

Figure 1: Schematic model of the routes of administration and the major barriers for drug absorption

In this thesis 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.

1.2.2. The difference between absorption and bioavailability

In literature, the terms drug absorption and bioavailability are both used in discussions on drug administration. Although strongly related, the two are essentially different (table 2). Absorption refers to transport over the absorbing membrane at the site of administration, whereas bioavailability is related to drug concentration in the systemic blood circulation. When the concentration in the blood plasma is measured as a function of time, the area under the curve represents the absolute bioavailability. The relative bioavailability, often reported in drug absorption studies, is calculated based on the comparison with the bioavailability after intravenous injection.

Bioavailability is affected by the intestinal and hepatic blood clearance of the drug. When the rate of clearance is linearly dependent on the blood concentration, absorption and bioavailability are proportionally related. However, when clearance processes take place via active secretion or via enzymatic metabolism, they can become saturated. In that case, intestinal and hepatic clearance depend on the blood concentration in a non-linear way or change in time which results in non-linear pharmacokinetics [14, 15]. When, in this situation, the absorption of a drug is increased to a certain extent, the bioavailability can increase more than proportional. Therefore, doubling the absorption can result in a more than double bioavailability.

To investigate drug absorption in-vitro colon adenocarcinoma (Caco-2) cells are used to form a selective barrier to model structure-transport relations for both passive as well as active transport [16]. To measure in-vivo absorption over the intestinal membrane, one should measure the concentration of drug immediately after the absorbing membrane or in the portal vein. This would yield information that is more closely related to the absorption of the dosage form [1]. To measure the bioavailability, one should measure the concentration of the drug in the systemic circulation. This would yield information that is more closely related to the therapeutic effect of the dosage form. This will lead to efficient development of drug products with optimal therapeutic effects.

Table 2: Differences between absorption and bioavailability

Absorption	Bioavailability
Strongly related to dosage form	Related to dosage form and clearance
Sometimes related to therapeutic effect	Strongly related to therapeutic effect
Dependent on transport over membrane	Dependent on both absorption and blood clearance

1.2.3. 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 (e.g. cyclodextrins) can be applied. Cyclodextrins are cyclic dextrins that have the most polar side of the glucose units oriented outwards, resulting in a more apolar cavity in which the hydrophobic drug can be entrapped [17]. They can increase the aqueous solubility of lipophilic molecules significantly. Moreover, cyclodextrin-drug complexes are solid at room temperature and can be used in solid dosage forms as well. Surfactants can form micelles entrapping hydrophobic molecules. Capsules can be used to deliver the drug in dissolved state to the gastro-intestinal tract, and surfactants keep the drug solubilized when it is exposed to the aqueous intestinal fluids. For example, this strategy has been successfully applied for danazol. The bioavailability of a capsule in which danazol was dissolved in Tween80® was increased 15.8 times compared to a powder filled capsule [18]. For a number of drugs, reproducible and extensive absorption after oral administration can be established by using surfactants [19, 20]. 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 highly undesirable [21]. Furthermore, due to the liquid state, molecular mobility is high and therefore in these formulations chemically unstable drugs are susceptible to degradation.

A third 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. THC, is dissolved. It is marketed in the USA as Marinol®. 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 will significantly decelerate the absorption. In-vivo studies indeed revealed that the onset of action of Marinol® capsules is very slow and that only a small amount of the drug reaches the systemic blood circulation [22, 23]. 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, stabilised by surfactant molecules [24]. Self-emulsifying or self micro-emulsifying drug delivery systems (SEDDS) form under conditions of mild agitation very fine dispersions (<100nm in diameter) [20]. SEDDS usually contain triglyceride oils and at least 25%w/w hydrophilic surfactants (HLB>11) and 0-50%w/w hydrophilic co-solvents [20, 25]. 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 [26].
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 will increase the surface area available for dissolution. According to the classical Noyes-Whitney equation this will increase the dissolution rate [27]. 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 [28-30], and they have proven to increase the amount of dissolved drug at the absorption site sometimes to supersaturated concentrations and consequently improve the bioavailability [2, 4, 6]. Solid dispersions are 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: the tablet.

1.3. Solid dispersions

1.3.1. Definition of solid dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [31]. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. They are described in Table 3. 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. Knowledge about the molecular arrangement will enlarge comprehension of the properties and behaviour of solid dispersions. Furthermore, it will facilitate optimization of their properties required for a specific application. For example, the mechanism underpinning the dissolution of solid dispersions is poorly understood [32]. 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 [33]. All three situations result in different drug concentrations at the dissolving interface [34]. 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. 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, the influence of drug load and method of preparation on dissolution behaviour and stability of solid dispersions can only be understood and predicted when the relation between these characteristics and the mode of incorporation is known.

Table 3: Classification of solid dispersions in six subtypes

SOLID DISPERSION TYPE		matrix *	drug **	remarks	no. phases	reference to literature
I	eutectics	C	C	the first type of solid dispersions prepared	2	[31], [35]
II	amorphous precipitations in crystalline matrix	C	A	rarely encountered	2	[36] [37]
III	solid solutions					
	continuous solid solutions	C	M	miscible at all compositions, never prepared	1	[31, 38]
	discontinuous solid solutions	C	M	partially miscible, 2 phases even though drug is molecularly dispersed	2	[35]
	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 discontinous: 2 phases even though drug is molecularly dispersed	1 or 2	[39, 40]
	interstitial solid solutions	C	M	drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinous. Example: Drug in helical interstitial spaces of PEG.	2	[31], [41]
IV	glass suspension	A	C	particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2	[31, 42-44]
V	glass suspension	A	A	particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2	[31, 43],
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	[44]

	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	[17, 45, 46]
	monotectics	C	C	same as eutectics but eutectic melting convergent with pure material, for completely non-interacting systems	2	[47, 48]
	co-precipitates	?	?	prepared by addition of non-solvent to solution of drug and matrix	?	[43, 44, 49]
	co-evaporates	?	?	prepared by vacuum drying, spray drying, freeze drying and spray-freeze drying, many examples	?	[50]

*: 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

1.3.2. Detection of crystallinity in solid dispersions

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions (see figure 2). 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 [33]. 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).

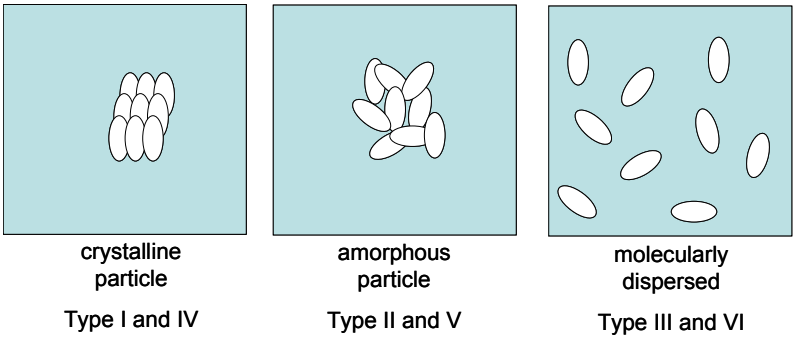

Figure 2: Schematic representation of three modes of incorporation of the drug in a solid dispersion.

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

1.) Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material. Recently developed X-ray equipment is semi-quantitative.
2.) Infrared spectroscopy (IR) can be used to detect the variation in the energy-distribution of interactions between drug and matrix [51]. 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 [53]. However in solid dispersions only qualitative detection was possible [54].
3.) Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different [55]. 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 [56]. 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 [57]. 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 [58] and proceeds to an unknown extent.
4.) Isothermal Microcalorimetry measures the crystallization energy of amorphous material that is heated above its T_g [59]. However, this technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.
5.) Dissolution Calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample[60]. 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.
6.) Macroscopic techniques that measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical

Analysis (DMA) determine the modulus of elasticity and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additivity of these properties in intimately mixed binary solids.

7.) The extent of supersaturation during dissolution experiments of solid dispersions are sometimes correlated to the mode of incorporation of the drug [61]. 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 can not be excluded that during dissolution crystallization of the drug occurs.

8.) A frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC) [62]. In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material. Possibly, the recrystallization energy can be used to calculate the amount of amorphous material provided, that all amorphous material is transformed to the crystalline state. If during DSC-measurements, amorphous material crystallizes, information is obtained on the crystallization kinetics and on the physical stability of the amorphous sample. To quantify the amount of crystalline material, measurements should be completed before crystallization of amorphous material has started. In some cases, this can be established applying high scanning rates.

Clearly, many techniques can distinct 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.

1.3.3. Detection of molecular structure in amorphous solid dispersions

The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix. The stability and dissolution behaviour could be different for solid dispersions that do not contain any crystalline drug particles, i.e. solid dispersions of type V and VI or for type II and III. However, not only the knowledge on the physical state (crystalline or amorphous) is important, the distribution of the drug as amorphous or crystalline particles or as separate drug molecules is relevant to the properties of the solid dispersion too. Nevertheless, only very few studies focus on the discrimination between amorphous incorporated particles (type II or V) versus molecular distribution or homogeneous mixtures (type III or VI).

1.) Confocal Raman Spectroscopy was used to measure the homogeneity of the solid mixture of ibuprofen in PVP [63]. 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 μm^3, uncertainty remains about the presence of nano-sized amorphous drug particles.

2.) Using IR or FTIR, the extent of interactions between drug and matrix can be measured. The interactions are indicative for the mode of incorporation of the drug, because separately dispersed drug molecules will have more drug-matrix interactions than when the drug is present in amorphous clusters or other multi-molecule arrangements [64, 65].

3.) Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. In case of amorphous matrices, TMDSC has been used to discriminate between solid dispersions type V and VI [66]. Furthermore, the value of the T_g is a function of the composition of the homogeneously mixed solid dispersion (see section 1.5.3). It has been shown that the sensitivity of TMDSC is higher than conventional DSC [67]. Therefore this technique can be used to assess the amount of molecularly dispersed drug [68], and from that the fraction of drug that is dispersed as separate molecules is calculated [69]. Moreover, the fraction of drug present in amorphous state can be assessed [70]. An example of a thermogram obtain from a TMDSC-experiment is shown in figure 3.

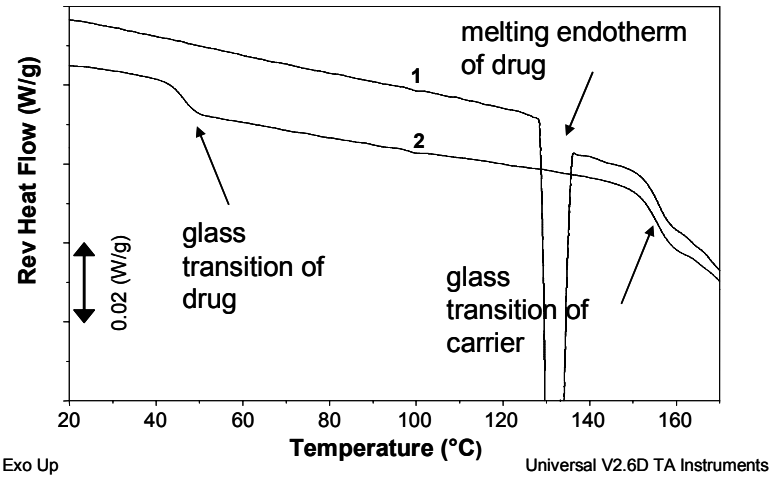

Figure 3: Example of a thermogram obtained with TMDSC: Trace 1: amorphous matrix containing crystalline drug particles. Trace 2: amorphous matrix containing amorphous drug particles.

1.4. Dissolution of solid dispersions

The mechanism of dissolution rate enhancement of a lipophilic drug incorporated in a solid dispersion is still to a large extent unclear. Publications on the fast release of drugs from solid dispersions are ubiquitous, but Craig [32] correctly stated that only few of them focus on the mechanism of release and the parameters that dominate the dissolution process. The influence of matrix-type is not fully understood. Moreover, the effect of drug load on the release rate of drugs from solid dispersions is ambiguous: in some studies a faster release of drug was observed upon lowering the drug load [30, 71, 72], while in other studies a faster release of drug was seen at higher drug-loads [73-75].

1.4.1. Dissolution of a pure solid

A description commonly used to explain the dissolution of a solid, was originally developed by Noyes and Whitney [27]. They claimed that the dissolution rate was proportional to the difference between bulk concentration and concentration at the dissolving interface. Nernst and Brunner [76] were the first to propose the diffusion layer model. 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. These assumptions are depicted in figure 4.

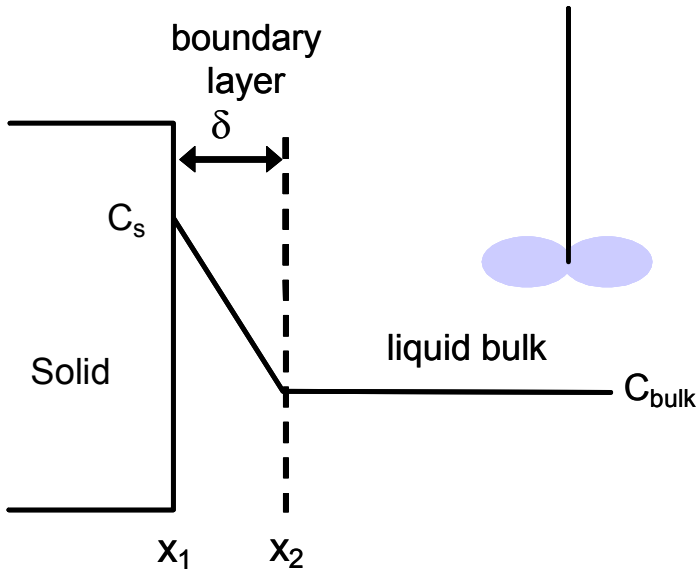

Figure 4. Schematic representation of dissolution of a solid

The dissolution rate of a solid is given by Eq. 1:

$$\frac{dm}{dt} = A\frac{D}{\delta}\left(C_s - C_{bulk}\right) \qquad \text{(Eq. 1)}$$

in which *dm/dt* is the dissolution rate ($kg \cdot s^{-1}$). In fact, all five parameters at the right-hand side of the equation can be affected in order to accelerate the dissolution rate:

1.) A represents the surface area available for dissolution. Micronization of drug particles increases the surface area and has been shown to accelerate dissolution [77]. 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 [31].

2.) A high diffusivity of the dissolving compound, D, establishes fast transport through the stagnant layer. The diffusivity in solutions can be calculated by the Einstein-Stokes relation:

$$D = \frac{kT}{3\pi\eta d} \qquad \text{(Eq. 2)}$$

in which η is the dynamic viscosity of the medium, i.e. the viscosity of the solvent in the boundary layer, and d is the diameter of the diffusing molecule, k is the Bolzmann constant and T is the temperature. Therefore, for a certain drug and temperature, only the viscosity of the medium can be used to change the diffusivity. Preferably, matrices that give only a minor or no increase in the viscosity in the boundary layer should be used.

3.) The thickness of the stagnant layer for diffusion δ should be minimized. This layer becomes thinner as the bulk surrounding the tablet is stirred more vigorously, e.g. in-vitro when the rotation speed of the impeller (ω in eq. 3 in s^{-1}) is increased or in-vivo when the intestinal mobility is higher. However, according to Nelson[78] also a low dynamic viscosity (η), and a high density (ρ) of the dissolution medium minimizes the diffusion-layer thickness:

$$\delta = \sqrt{\frac{\eta}{\rho\omega}} \qquad \text{(Eq. 3)}$$

4.) An increase in drug solubility (C_s) accelerates the dissolution. Solubilizers like cyclodextrins or surfactants are added to solid dispersions for this purpose. C_s is also increased by reducing the size of the particles according to Kelvin's Law [79]:

$$C_{s,curved} = C_{s,flat} \cdot exp\left(\frac{2\gamma_{d,s}M_d}{RT\rho_d r}\right) \qquad \text{(Eq. 4)}$$

in which $\gamma_{d,s}$ is the interfacial tension of the drug-solution interface, M_d is the molar mass of the drug, ρ_d the density of the drug and r the radius of curvature of the dissolving interface. Thus, Eq. 12 provides the second reason for reducing the drug particle size. Furthermore it is known that amorphous material has a higher solubility than a crystalline material [80]. The higher solubility of amorphous drugs can be expected based on thermodynamical considerations and was confirmed with experiments [34, 60, 81]. For example, amorphous novobiocin showed a 10 times higher equilibrium solubility compared to the crystalline form [36].

5.) 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.

1.4.2. Dissolution of a binary solid

The Nernst-Brunner equation (Eq.1) is applicable for pure solids but the dissolution of a binary solid is more complex. The dissolution rate of two components, intimately mixed in solid dispersions, mutually affect each other. Higuchi [82] investigated a uniform, intimate, non-disintegrating mixture of two dissolving compounds both in crystalline state. One of the compounds (e.g. the matrix: C) dissolves faster, resulting in a porous layer consisting of the other compound (e.g. the lipophilic drug: D) (see figure 5).

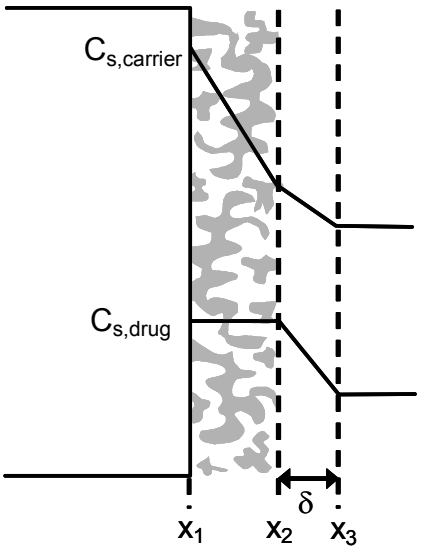

Figure 5: Schematic representation of dissolution of a binary mixture.

Higuchi investigated the effect of this layer and the composition of the mixture on the dissolution rate of the fast dissolving component C. In fact, the deceleration of the dissolution of C was discussed while dissolution of D was considered to remain unchanged. He considered only the steady state portion of the problem and assumed that in the porous layer the concentration of D is equal to its solubility ($C_{Drug} = C_{s,Drug}$). This implies that no supersaturation of D occurs in the liquid compartment of the porous layer. It also implies a constant flux of D to the bulk, since the thickness of the stagnant boundary layer δ will be constant [82]. It is unlikely that amorphous solid dispersions can be described in this way: firstly because D will be supersaturated during dissolution of a solid dispersion. Without supersaturation it is impossible to obtain accelerated dissolution from a non-disintegrating solid dispersion tablet. A second complication is that the degree of supersaturation can increase in time especially when C dissolves rapidly. And thirdly, due to this supersaturation, crystallization of the lipophilic drug at the tablet surface can occur. It has been observed that crystallization can influence dissolution behaviour of solid dispersions [71, 72, 83-85]. Both supersaturation and crystallization kinetics will affect the time needed to reach steady state dissolution. It has been described that the initial non-steady state portion of the problem, assumed to be negligible in Higuchi's description, in fact largely determines the dissolution rate especially when a large solubility difference exists between matrix and drug [82, 84].

1.5. Physical stability of amorphous solid dispersions

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 themodynamically unstable. In solid dispersions containing crystalline particles (type IV, section 1.3.1), 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 [86]. 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 figure 6.
The physical stability of amorphous solid dispersions should be related not only to crystallization of drug but 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.

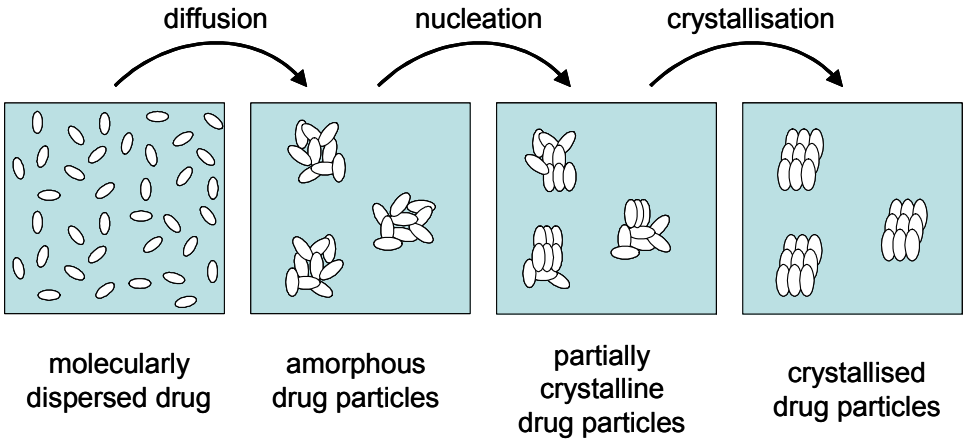

Figure 6: Physical changes in solid dispersions resulting in crystallization

1.5.1. Physical properties of the amorphous state

Materials can occur in different states. The crystalline state and the liquid state above the melting temperature (T_M) are thermodynamically stable. 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 kinetic stability of amorphous material depends on the physical state of the material. Two physical states can be defined for amorphous material: the glassy state and the rubbery state. Table 4 shows the most relevant characteristics of the various thermodynamically stable and unstable states that materials may occur in.

Table 4: Characteristics of thermodynamically stable and unstable physical states of material.

Thermodynamically stable	
Crystall	Liquid
• Below the melting temperature • Molecules in crystalline lattice • Low molecular mobility (no translations, only rotations and vibrations)	• Above the melting temperature • Molecules randomly orientated • High molecular mobility (including translations)
Thermodynamically unstable	
Glass	Rubber/super-cooled liquid
• Below the glass transition temperature • Molecules randomly distributed, liquid-like • Low molecular mobility • Kinetically stable • Crystallization and chemical reactions are absent or extremely slow	• Above the glass transition temperature • Molecules randomly distributed, liquid-like • High molecular mobility • Kinetically unstable • Crystallization and chemical reactions can be observed

At the glass transition temperature (T_g), the following properties change dramatically: modulus of elasticity (E), dynamic viscosity (η), specific volume (V), enthalpy (H), specific heat (C_p) and thermal expansion coefficient (α). In contrast to first-order transitions like melting, where properties abruptly change, at a second-order transition only the first derivative of a property changes [87]. For

example, the thermal expansion coefficient (α) and the specific heat (C_p) change at T_g according to:

$$\alpha = \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_p \quad \text{(Eq. 5)}$$

$$C_p = \left(\frac{\partial H}{\partial T}\right)_p \quad \text{(Eq. 6)}$$

Therefore, the T_g is a second-order transition. In figure 7, the specific volume and enthalpy of an amorphous solid is depicted.

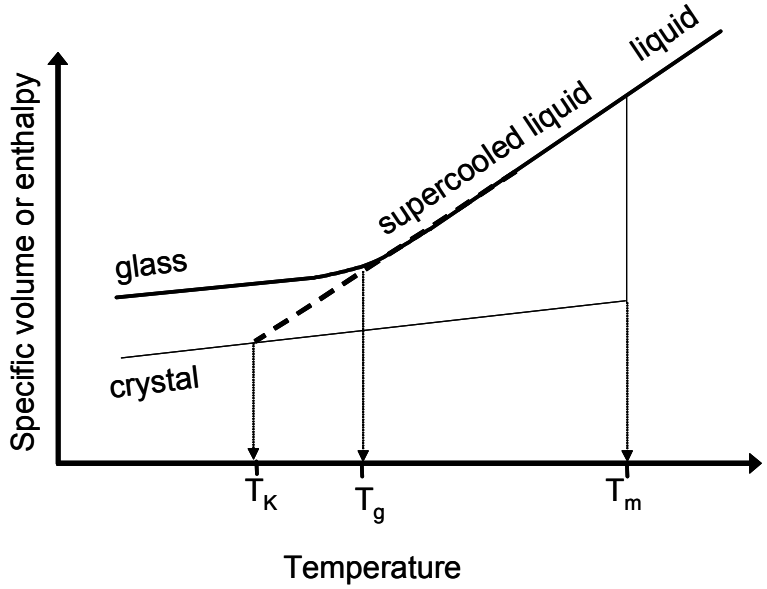

Figure 7: Specific volume or enthalpy as a function of temperature for amorphous materials (thick line) compared to crystalline material (thin line). T_K is the Kauzman temperature.

1.5.2. Molecular mobility in amorphous solids

The molecular mobility in amorphous materials determines the physical stability and reactivity. The molecular mobility is related to macromolecular properties like viscosity but is generally quantified in terms of mean relaxation time τ. The relaxation time is defined as the time necessary for a molecule or chain segment to diffuse across the distance of one molecule or chain segment. The relaxation time varies with temperature. Typical relaxation times at T_g are 100-200 seconds [88, 89]. As a rule of thumb, the risk of crystallization during glass formation is minimized when relaxation times are similar or larger than experimental time frames, like a drying- or cooling-period. Relaxation times at the storage conditions will be indicative for shelf life. Molecular relaxation times can be characterized by the change of several bulk properties like enthalpy or volume in time. The extent of

relaxation is described empirically by the Kohlrausch-Williams-Watts equation (Eq. 7), as discussed by Hodge [88]:

$$\phi(t) = exp\left[-\left(\frac{t}{\tau}\right)^{\beta}\right] \qquad 0 < \beta \leq 1 \qquad \text{(Eq. 7)}$$

in which $\varphi(t)$ can be considered as the fraction of non-relaxated material at time t and β is the relaxation time distribution parameter which is a function of temperature. The practical application of this equation to characterize relaxation processes in different glasses was shown in a study by Six et al. [90]. When the mean relaxation time and the relaxation time distribution parameter β are known, a shelf life could be predicted. When it is assumed that for example maximally 10% of the product may reached a relaxed state, i.e 10% degradation or 10% crystallization, $\varphi(t)$ must be at least 90% [91].

Some amorphous materials show non-Arrhenius behaviour since at temperatures just above T_g, τ decreases typically by a factor of 10 for every 3K temperature rise. For amorphous materials showing Arrhenius behaviour this would be require a 33K temperature change [89]. The temperature dependency of the relaxation time is closely related to viscosity of amorphous solids and hence both properties can be plotted in one graph. Figure 8 shows the molecular relaxation time and the viscosity for two types of amorphous materials: strong glasses and fragile glasses. This subdivision of amorphous materials, proposed by Angell [92], is based on the temperature dependence of relaxation time or viscosity above its T_g. The strong glasses show Arrhenius behaviour, whereas fragile glasses show strong non-linearity in the viscosity (or relaxation) versus temperature plot, indicating significant deviation from the exponential Arrhenius relation. Fragile glasses above their T_g can be described by the empirical William-Landel-Ferry (WLF) equation [93]:

$$log\left(\frac{\eta_T}{\eta_{Tg}}\right) = -\frac{C_1 \cdot (T - Tg)}{C_2 + (T - Tg)} \qquad \text{(Eq. 8)}$$

describing the viscosity η at temperature T and T_g. For polymers with $T_m/T_g \approx 3/2$, the viscosity obeys the WLF-equation with constants C_1 and C_2 of 17.44 and 51.6 respectively, which are therefore referred to as 'universal' constants [89]. Moreover, the Vogel-Tammann-Fulcher (VTF) equation can be used to model the behaviour of amorphous solids:

$$\tau = \tau_0\, exp\left(\frac{DT_0}{T - T_0}\right) \quad \text{and} \quad \eta = \eta_0\, exp\left(\frac{DT_0}{T - T_0}\right) \qquad \text{(Eq. 9)}$$

with T_0 and D constants. T_0 is the temperature at which either τ or η become infinite. T_0 is conceptually related to T_K, the Kauzmann temperature (see below). D represents the strength parameter and is larger for stronger glasses. D-values smaller than 10 indicate fragile behaviour, whereas D-values larger than 30 indicate strong behaviour and easy vitrification. It should be noted that the

viscosity and relaxation time decrease more rapidly in fragile materials. This implies that strong glasses will be more stable and devitrification or crystallization proceeds slower. Unfortunately, it seems that most pharmaceutical amorphous systems show moderately fragile to fragile behaviour [94].

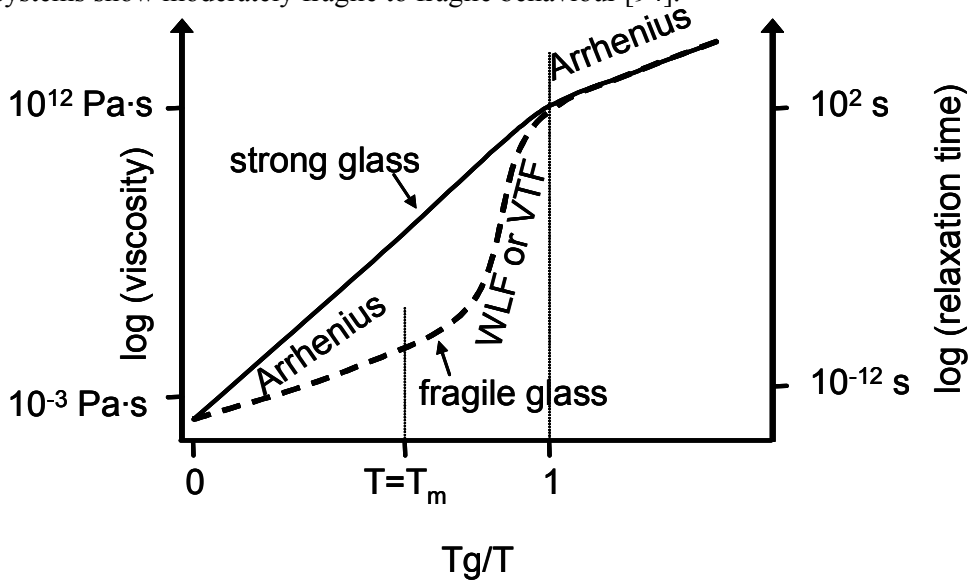

Figure 8: Viscosity and relaxation time as a function of temperature relative to T_g. The solid line represents a strong glass and the dashed line represents a fragile glass. Strong glasses can be described by the Arrhenius equation. Fragile glasses can be described by the William-Landel-Ferry (WLF) equation or by the Vogel-Tammann-Fulcher (VTF) equation at temperatures between T_m and T_g. Above the T_m or below the T_g a fragile glass can be described by the Arrhenius equation. Values for the viscosity and relaxation times are typical values as reported in various studies [88, 92, 94, 95]

Figure 8 shows that the T_g represents an important demarcation between high and low mobility. However, storage at sub- T_g temperatures is by no means an absolute guarantee for complete prevention of crystallization or chemical degradation [96]. The thermodynamic or ideal T_g with zero excess properties is referred to in literature as the Kauzmann temperature T_K [97] or T_0, the temperature of zero mobility. It is defined as the temperature at which the excess or configurational entropy of the supercooled liquid would reach zero and the total entropy would approach that of a crystal. A method to measure T_K has been developed and reported in an application note [98]. In some studies a T_g -50 rule has been proposed, and it is claimed that for most fragile glasses, T_K is approximately 50 degrees below the T_g [96]. To apply this rule to solid dispersions of type VI, the T_g of the pure matrix material (without drug) is irrelevant. The T_g of the sample (matrix containing the drug) at the storage condition should be used, which can be different from the matrix T_g due to other molecules, e.g. an incorporated drug or absorbed water acting as plasticizer.

1.5.3. Molecular mobility in drug-matrix mixtures: anti-plasticization approach

Another way of looking at molecular mobility in amorphous solid dispersions is by investigation of the anti-plasticizing of the drug by the matrix. When drug and matrix are mixed homogeneously, the solid dispersion consists of one amorphous phase (type VI, table 2). By addition of the matrix, usually having a higher T_g, the T_g of the solid dispersion is elevated compared to that of the drug alone. Accordingly, the molecular mobility of the drug has been reduced [99]. This anti-plasticization approach, although reported as separate stabilization mechanism [33], is essentially the same as T_g -dependent mobility reduction, described in section 1.5.2. It is obvious that the T_g of the matrix should be as high as possible in order to obtain a solid dispersion with a high T_g and thus a low molecular mobility. In this respect, the plasticizing effect of water absorbed in solid dispersions should be considered as well. Many matrices are hygroscopic and water will be homogeneously distributed through the solid dispersion. The T_g of the matrix can be decreased to below storage temperature and the material becomes prone to devitrification. The plasticizing capacity of water is huge due to its low T_g, i.e. 135(K). It can be concluded that the T_g of an homogeneous solid dispersion determines its stability. The T_g of these solid dispersions can be predicted with the Gordon-Taylor equation [100]:

$$T_{g,MIX} = \frac{T_{g,D} \cdot w_D + T_{g,C} \cdot K \cdot (1 - w_D)}{w_D + K \cdot (1 - w_D)} \qquad \text{(Eq. 10)}$$

in which $T_{g,MIX}$ is the glass transition of the solid dispersion, $T_{g,D}$ and $T_{g,C}$ are the T_g ´s of drug and matrix respectively and w_D is the weight fraction drug. The constant K according the Simha-Boyer rule [101] is given by:

$$K = \frac{\rho_D \cdot T_{g,D}}{\rho_C \cdot T_{g,C}} \qquad \text{(Eq. 11)}$$

in which ρ_D and ρ_C the density's of drug and matrix, respectively. Ten Brinke and co-workers assumed that the change in specific heat of glass and rubber (ΔC_p) was inversely proportional to temperature [102] resulting in a different definition of the constant K:

$$K = \frac{\Delta C_{p,C}}{\Delta C_{p,D}} \qquad \text{(Eq. 12)}$$

Obviously, the stability of amorphous solid dispersions that consist of two phases is determined by the mobility in those two phases. For example, in an amorphous solid dispersion containing amorphous clusters of drug molecules, the diffusion of drug in the matrix is determined by the T_g of the matrix, whereas crystallization of molecules within the clusters will be mainly determined by the T_g of the drug. Only

at the cluster-matrix interface, the matrix is capable of stabilizing the drug. Therefore, in this type of solid dispersions, the size of the amorphous drug clusters will affect the crystallization rate to a significant extent.

1.5.4. Effect of molecular properties on crystallization

The rate of crystallization of an amorphous material, e.g. a drug, is determined by two distinct processes: nucleation and propagation, i.e. the growth of nuclei to form crystals. Nucleation proceeds faster at lower temperatures, whereas propagation is favoured by high molecular mobility, obtained at elevated temperatures. This results in an overall crystallization rate as depicted in figure 9.

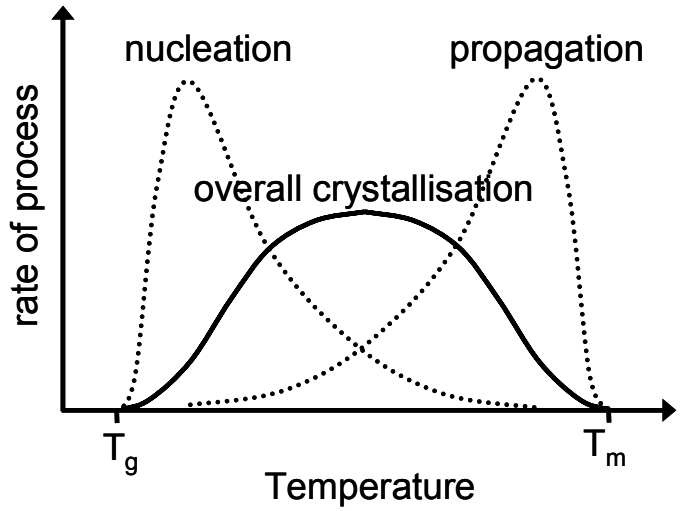

Figure 9: Overall crystallization rate as a function of temperature. T_g is the glass transition temperature and Tm is the melting temperature. Adapted from [89].

The crystallization rate also depends on the drug molecule itself. Most lipophilic drugs easily crystallize and therefore occur generally in the crystalline state. However, some molecules like cyclosporine A form a liquid crystal with molecular regularity in only two dimensions [103], or lipophilic resins like Δ^9-tetrahydrocannabinol (THC) simply resist crystallization [104]. Similarly, the matrix PVP resists crystallization, whereas for example PEG and mannitol easily crystallize. It was found that the extent of relaxation in glassy drugs was dependent on the complexity of the molecular structure of the drug molecule [90]. Furthermore, Hancock and Zografi concluded that crystallization of the drug is dependent on molecular size, complexity, shape and orientation of the molecules in the crystalline lattice [80].

1.5.5. Drug-matrix mass ratio

Several aspects determine the effect of amorphous solid dispersion composition on physical stability. Firstly, the diffusion distance for separate drug molecules to form amorphous or crystalline particles is larger for lower drug contents. Hence, the formation of a separate drug phase is significantly retarded. Secondly, low drug contents minimize the risk of exceeding the solid solubility [69]. When the solid solubility is lower than the drug load, there is a driving force for phase separation. This is only relevant for drug-matrix combinations that are partially miscible or immiscible. Thirdly, the T_g of a homogeneous solid dispersion is a function of the composition (See Eq. 10). When the drug has a lower T_g than the matrix, a high drug content depresses the T_g of the solid dispersion, increasing the risk for phase separation. And finally, if drug-matrix interaction increases stability, then also low drug contents are preferred, since in that case drug-drug contacts will be rare and drug-matrix contacts omnipresent. These arguments favour the choice of low drug content. However, a high drug content can decrease the hygroscopicity of the solid dispersion and enables the preparation of a high dosed dosage forms. The drug, being hydrophobic in nature, is generally less hygroscopic than the matrix. Molecularly incorporated drug reduces the amount of water that can plasticize the solid dispersion when exposed to a particular relative humidity, thereby decreasing molecular mobility [57]. Therefore, more drug can not only reduce the T_g of the dry solid dispersion but also decrease the plasticizing effect of water. Which one of the two competing effects has a larger contribution is difficult to predict. A second reason for increased stability with increasing drug loads, is the inhibition of crystallization of the matrix above a certain drug load, when drug molecules sterically block the migration of matrix molecules [58]. Table 5 summarizes the effects of an increased drug load.

Table 5: Effects of an increased drug-matrix mass ratio (i.e. drug load) on physical stability

Increasing drug load deteriorates physical stability because:
• it alters (generally decrease) the T_g of a homogeneous solid dispersion • it reduces the distance between drug molecules and hence facilitates crystallization.
Increasing drug load improves physical stability because:
• it reduces hygroscopicity and hence reduce plasticizing effect of water (especially for homogeneous solid dispersion) • it prevents crystallization of the matrix and hence inhibits phase separation

1.5.6. Matrix molecular weight

To develop a stable solid dispersion, the molecular mobility should be minimized. As concluded in section 1.5.2, matrices with a high T_g are preferred. The selection of high molecular weight matrices is suitable for that purpose, because the free volume is smaller implying that molecular motions are restricted. The relation between high molecular weight and high physical stability is generally acknowledged in solid dispersion literature [33]. In most studies, physical stability is suggested only because dissolution profiles remain constant after storage.

The T_g of an amorphous matrix increases with increasing molecular weigth. Higher temperatures are allowed before transition takes place from the glassy, low mobility state to the rubbery state in which drug molecules can diffuse and crystallise. The T_g has a certain maximum value, depending on the monomer. The relation between T_g and molecular weight is described by the Fox-Flory equation [105]:

$$\frac{1}{T_g} = \frac{1}{T_g^{\infty}} + \frac{K}{DP} \qquad \text{(Eq. 13)}$$

In which T_g^{∞} is the T_g at infinite chain length, K is a constant that depends on monomer geometry and interactions and DP is the degree of polymerization. The effect of molecular weight of PEG and PVP, was investigated in relation to their dissolution behaviour: slow dissolution was attributed to crystallization. Furthermore, gel formation of high molecular weight matrices can decelerate dissolution [75]. the effect of molecular weight on physical stability during storage is scarcely investigated. It was found that low molecular weight PVP did not prevent crystallization, whereas longer chains did [106]. Therefore, low molecular weight matrices are mixed with large matrix molecules to obtain high physical stability [107].

1.5.7. Drug-matrix interactions

Drug-matrix interaction is relevant during preparation and dissolution of solid dispersions. The extent and type of interactions govern miscibility during fusion, dissolution in a common solvent, phase separation and dissolution of the dosage form. Furthermore, drug-matrix interactions determine the physical stability of solid dispersions during storage. For example, H-bonding with PVP is often related to physical stabilization [108, 109] [51, 54]. Efficient insertion of the labile quinapril in the cavity of cyclodextrins resulted in chemical stabilization by complexation [64]. Furthermore, the photostability of nifidipine could be increased by incorporation in cyclodextrin cavity as well [17].

Another consequence of drug-matrix interactions is an increase of T_g to values higher than predicted by the Gordon-Taylor equation. Restricted molecular mobility increases the T_g to levels above the T_g's of the individual components. Borax (when molecularly incorporated) is know to increase the T_g and T_g' of sugar

matrices [110]. It is claimed that strong interactions present during complex formation increase the T_g and hence increased physical stability [111, 112].
However, discussions are ongoing, which aspect more contributes to stability: drug-matrix interactions or the anti-plasticizing effect, i.e. a high T_g of the matrix [113]. When the monomer of PVP, vinylpyrollidone, was compared with PVP, drug-matrix interactions are the same, but physical stability was lost using the monomer [106]. To differentiate between the two aspects, it would be of interest to compare the physical stability of solid dispersions with the same T_g's but different interactions.

1.6. 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 [31, 35]. 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.

1.6.1. 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. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix [35] which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions of type I (see section 1.3.1). Poly(ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG. The helices are aligned in orderly fashion, illustrating that PEG easily crystallizes. Another polymer frequently applied as a matrix in the fusion method is poly(vinyl pyrollidone) PVP. PVP, supplied in the amorphous state, is heated to above its T_g. The drug has to fuse with or dissolve in the rubbery

matrix, which is subsequently cooled to vitrify the solid dispersion. When PVP is used as matrix, solid dispersions of type V or VI are obtained. The mode of incorporation of the drug depends on the PVP-drug miscibility and the preparation procedure. Grinding is required to obtain the solid dispersion as powder that is easy to handle.
Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture [114, 115], which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants [116, 117].
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 [118, 119]. 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 [120] 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.

1.6.2. Hot melt extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar [121], but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms [37]. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid-state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials [122, 123]. 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.

1.6.3. 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 (see section 1.4). 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 [124], 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 [125, 126], but this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical. Solubilisers like cyclodextrins or surfactants like Tween80® increase the aqueous solubility of the drug substantially. However, the amount of solubilisers or surfactants in the final product are often eminent. This results in solid dispersions that, to a significant extent, consist of solubilisers or surfactants, materials that significantly change the physical properties of the matrix (e.g. decrease of T_g). 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 [127] or dichloromethane [116] have been used to dissolve both drug and PVP as matrix simultaneously. These solvents are used also in other preparation methods (see below). However, according to the ICH-Guidelines [128], these solvents belong to Class I, comprising the most toxic solvents. Therefore, the use of these solvents is unacceptable and impractical because the amount of residual solvent present in the solid dispersion after drying has to be below the detection limits. The last strategy for the dissolution of both drug and matrix is the use of solvent mixtures. Water and ethanol [29], or dichloromethane and ethanol [68] 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). This is depicted in figure 9.

To dry the solutions, vacuum drying is often used [28, 49]. The solution is dried by the application of vacuum and moderate heating. Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. Afterwards the formed solid dispersion is often stored in a vacuum desiccator to remove the residual solvent. Vacuum drying at elevated temperature bears the risk of phase separation because the mobility of drug and matrix decreases slowly. Another drying technique is spray drying. The solution is dispersed as fine particles in hot air. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Moreover, the solid dispersions prepared by spray drying consist of particles of which the size may be customized by changing the droplet size to meet the requirements for further processing or application (e.g. free flowing particles or particles for inhalation). Spray drying usually yields drug in the amorphous state [50], however sometimes the drug may have (partially) crystallized during processing [86].

An alternative to these drying techniques is freeze drying. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices [129], the technique is poorly exploited for the preparation of solid dispersions [127, 130, 131]. One of the reasons might be the low freezing temperature of most organic solvents (see table 4). 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 T_g of the maximally freeze concentrated fraction. Therefore, low sample temperatures are required which slows down the process. Betageri and Makarla [127] used a condenser temperature of -75°C, to dry a solution with cyclohexanol as the solvent. In table 6 an overview is presented of several organic solvents. To obtain a lyophiliation process of acceptable duration, the solvent should have a sufficiently high vapour pressure. As can be seen in table 6, dimethylsulphoxide DMSO has a high melting temperature but it has a very low vapour pressure. Therefore, DMSO is not suitable as a solvent for freeze drying.

Table 6: Atmospheric melting and boiling temperature and vapour pressure of organic solvents

solvent	melting point (°C)	boiling point (°C)	vapour pressure at 25°C (kPa)
water	0	100	3.16
methanol	-93.9	65	16.9
ethanol	-117	78.5	5.79
1-propanol	-85.8	97.4	2.27
2-propanol	-127	82.4	5.85
chloroform	-63	62	26.1
Dimethylsulphoxide(DMSO)	19	189	0.08
acetic acid	17	118	1.64
1,4-dioxane	12	102	4.92
2-methyl-2-propanol (TBA)	25	82	5.49

A suitable solvent that meets both requirements is 2-methyl-2-propanol or tertiary butanol (TBA), because it has a high melting temperature as well as a high vapour pressure. The application of TBA in lyophilization is discussed by Teagarden [132]. Also mixtures of solvents can be considered. However, in that case the phase diagram of the mixture should be consulted. For example, while water and DMSO have melting points of 0°C and 19°C, the mixture has eutectic points below -60°C. The sample temperature of such a mixture should be kept below this value, which causes a slow sublimation.

An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified.
An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum [65, 133-135]. 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 [136], or nasal administration [137].

1.6.4. Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent [138, 139]. When supercritical CO_2 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 CO_2 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 CO_2 of most pharmaceutical compounds is very low (<0.01wt-%) [140] and decreases with increasing polarity [138]. Therefore, scaling up this process to kilogram-scale will be impractical.
All other supercritical techniques are precipitation methods. Although generally labelled as solvent-free, all these supercritical fluid methods use organic solvents to dissolve drug and matrix and exploit the low solubility of pharmaceutical compounds in CO_2. In fact, these techniques represent alternative methods to remove solvents from a solution containing typically a drug and a polymer. Moneghini and co-workers [141] 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 CO_2. The conditions are chosen so that CO_2 is completely miscible with the solution under supercritical conditions, whereas drug and matrix will precipitate upon expansion of the solution. When the volume of the solution expands the solvent strength (i.e. the ability to dissolve the drug) decreases. This results in precipitation of matrix and drug. Since this technique is often applied with PEG as matrix, this technique results in formation of a solid dispersion with a crystalline matrix (mostly type II or III) [130].
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) [140]. More specific examples of PCA are Supercritical AntiSolvent (SAS) when supercritical CO_2 is used, or Aerosol Solvent Extraction System (ASES), and Solution Enhanced Dispersion by Supercritical fluids (SEDS) [138, 140]. However, as with the other solvent techniques described in the previous section, the critical step in these precipitation techniques might be the dissolution of drug and matrix in one solution. The use of water is limited, because the water solubility in compressed CO_2 is limited [43]. Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix [142].

1.6.5. 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 [43].

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 is investigated for poly(methyl methacrylate) [143] 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 [130]. After rapid evaporation of the solvent, the fibres can be directly used or milled and further processed [144].

1.7. Unmet needs and challenges

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

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

Ritonavir capsules (Norvir, Abbott) has been withdrawn temporarily from the market because of crystallization [130]. The rare occurrence of solid dispersion-based pharmaceutical dosage forms in the clinic are due to problems in scale-up of preparation methods, difficulties in dosage form development and poor and irreproducible physical and chemical stability of drug and matrix [83].

Knowledge about the behaviour of solid dispersions during preparation, storage and dissolution can help to tackle these problems. A thorough understanding of processes that occur place on the molecular level is a prerequisite for rational and more efficient design of solid dispersions. However, development of solid dispersions has often been a trial-and-error approach. Unfortunately, most reports deal with a case, in which the authors used a specific matrix to accelerate the dissolution of a specific drug in-vitro or to show increased bioavailability. These studies prove the potential of solid dispersions but for successful industrialization and clinical application, the following challenges have to be faced first.

1.7.1. Exploring characterization tools

Any study on solid dispersions requires physical and/or chemical characterization. During or after preparation, during stability studies and during dissolution experiments, knowledge of the physical and chemical state of matrix and drug and changes thereof is indispensable.

Currently, characterization tools of amorphous solid dispersions are poorly developed [33]. The T_g can be characterized with Differential Scanning Calorimetry (DSC), but standardization of the scanning rate is required, since this can affect the outcome of the measurement [62]. Furthermore, a technique is needed to measure the distribution in solid dispersions, i.e. separate molecules, homogeneously distributed, amorphous clusters or crystalline particles. Such a technique should be non-invasive for the sample, maintaining the molecular structure during the measurement. Furthermore, it should be noted that due to the lack of proper characterization tools, dissolution experiments are mistakably used for this purpose. Sometimes physical stability is proven by an unchanged dissolution rate without any elucidation of the molecular structure. Studying either physical stability or dissolution behaviour requires proper characterization methods.

1.7.2. Meeting conflicting requirements for the matrix

The current problems during preparation of solid dispersions are partially due to the conflicting requirements for easy production, low hygroscopicity, high stability and fast dissolution. A stable amorphous solid dispersion has a matrix with low molecular mobility. This is achieved by choosing a matrix with a high T_g and hence preferably a high molecular weight. However, mixing a high molecular weight hydrophilic matrix with a lipophilic drug requires higher temperatures when the fusion method is applied. When the solvent method is applied, it will be more difficult to find a common solvent for matrix and drug. By reducing the polarity of the matrix, these difficulties could be avoided. However, at this moment it is assumed that increased dissolution is obtained by increased wetting of the hydrophobic drug. Therefore, the matrix should have a high polarity to be compatible with the aqueous environment. A possible problem of a polar matrix is the hygroscopicity, which deteriorates the physical stability. Furthermore, it can be expected that a polar matrix and a lipophilic drug are more susceptible for phase separation during preparation and storage. Clearly, the quest for the ideal matrix is complicated but realizing these issues will help in the rapid recognition of an appropriate compromise.

1.7.3. Finding an adequate production process

Although the versatility and robustness of a production method depends on the properties of the matrix and the limitations imposed by the drug, the following general advice can be distilled from literature. Once drug and matrix are fused or together dissolved in one solution, a fast cooling or rapid immobilization (vitrification) is beneficial to prevent phase separation, e.g.: [31, 35, 43]. Therefore, quench cooling or rapid evaporation processes like spray drying, supercritical drying and fast freezing methods using liquid nitrogen should be considered.
Other considerations involving production methods are:

1.) The poor reproducibility of the physical properties of solid dispersions should be improved by investigating the effect of process parameters in depth.
2.) Degradation of thermo-labile drugs should be prevented by exploring low temperature preparation methods like the solvent method combined with freeze drying.
3.) For the solvent method a suitable solvent or solvent mixture should be found, that is capable of dissolving significant amounts of both drug and matrix, easy to remove and low in toxicity.
4.) The effect of process conditions on the amount of residual solvents should measured.

1.7.4. Need for 'engineering' approach

Stability is regarded as the net result of molecular mobility processes like rearrangements, crystallization and diffusion. Currently, a debate is going on about

what affects these processes most: maintaining of the position of molecules by the matrix (e.g. high T_g) [113] or by interactions between drug and matrix [108]. Furthermore, drug-matrix miscibility should be considered beforehand, because a poor miscibility implicates a large driving force for phase separation. By using the Hildebrand solubility parameters [114] or Hanson solubility parameters [123], the miscibility, solid solubility and the formation of a solid solution can be predicted. Phase diagrams for drug-matrix systems and calculation of thermodynamic properties like the change in Gibbs-Free energy of mixing drug and matrix can be useful in this respect. Hancock pleads for an ´engineering´ approach rather than the current empirical approach [91]. This means that crystallization of the drug in the solid dispersion should be steered after the elucidation of the effect of critical parameters like T_g, miscibility and drug-matrix interaction.

1.7.5. Understanding dissolution behaviour

The objective to prepare solid dispersion is often to accelerate the dissolution of a lipophilic drug in aqueous environment. Because many studies have shown the potential of solid dispersion technology, the processes during dissolution need to be studied and discussed. The effects of mode of incorporation, matrix properties and drug load need to be investigated in more detail [32, 145]. Especially their effect on processes during dissolution needs to be considered, e.g. in some studies [72, 85] it has been found that the drug (partially) crystallized in the diffusion layer during dissolution. Obviously, this phenomenon affects release of the drug to the bulk and therefore deserves major attention.

1.7.6. Application of solid dispersions in dosage forms

The formulation of solid dispersions into drug administration forms also presents a great challenge. Essential steps like milling, sieving or granulation can affect the properties of the solid dispersion. Stress induced crystallization has been observed for amorphous trehalose glasses resulting in degradation of the incorporated protein [129]. Therefore, sugars with low crystallization tendency are preferred. Furthermore, many dissolution studies are performed with powders or grinded solid dispersions, instead of tablets. This is probably because disintegration of the tablet is problematic. Many matrices become waxy and sticky or even melt during tablet compaction. The two most used matrices, PEG and PVP, have very good binding properties. Moreover, they fill up the pores during the compaction process thereby hindering rapid dissolution of the tablet. Sometimes capping is caused by the elastic behaviour of completely dry amorphous materials [129]. The use of other excipients to prepare solid dispersion tablets with high tensile strength and proper dissolution and disintegration properties should be investigated. Finally, the application of fast release solid dispersions for non-oral routes needs to be investigated. The fast release of a highly lipophilic drug in the pulmonary mucosa could lead to rapid local action or rapid systemic absorption.

1.8. Scope of this thesis

The research described in this thesis was focussed on solid dispersions of poorly water soluble lipophilic drugs in matrices of amorphous sugars. Some of the lipophilic drugs were also chemically unstable. PVP matrices were used as reference material to compare different aspects related to preparation, characterization and dissolution. In chapter 2, a novel method is described to prepare fully amorphous solid dispersions based on sugar glasses containing lipophilic drugs. The preparation method is a solvent method, which is suitable for use in combination with low temperature drying, like freeze drying. The versatility of this technique is investigated by preparing solid dispersions with various drugs, various matrices and various drug loads. The following sugar matrices were tested: sucrose, trehalose, and the oligo-fructose inulin with two different chain lengths. Their physical stabilising capacity for a model drug (diazepam) in relation to their T_g is tested. In the last part of this chapter, the amount of residual organic solvent is investigated. The effect of several process parameters is discussed.
Chapter 3 deals with the dissolution behaviour of sugar glass dispersion tablets. The sugar glass dispersions are produced according to the procedure described in chapter 2. The dissolution of amorphous solid dispersion tablets is compared to tablets consisting of the corresponding physical mixtures. Again, four different matrices are used: sucrose, trehalose and two inulins with different chain lengths. The effect of the matrix type and drug load is investigated. The dissolution behaviour is thoroughly investigated by measuring the dissolution of drug and matrix simultaneously. A new mechanism is proposed to describe the dissolution of solid dispersions.
Chapter 4 explores the application of Temperature Modulated Differential Scanning Calorimetry (TMDSC) for the characterization of fully amorphous solid dispersions. Two matrices are compared: inulin, and PVP being the commonly used matrix for amorphous solid dispersions. The detection of molecularly dispersed drug and amorphous drug clusters is investigated. The change in specific heat at the glass transition as well as the value of the T_g is used to assess the amount of drug that is present in clusters. The effect of matrix type and freezing rate is investigated. Furthermore, water vapour sorption of both inulin and PVP solid dispersions is measured. The disproportional decrease in hygroscopicity of PVP is used to estimate the size of amorphous drug clusters.
In chapter 5, a new method is proposed to detect amorphous nano-sized clusters of lipophilic molecules. The use of fluorescent resonance energy transfer FRET is described. It is investigated what experimental setup would yield information on the mode of incorporation of lipophilic molecules in fully amorphous solid dispersions.
Chapters 6 and 7 present two examples of the application of sugar glass dispersions in the formulation of dosage forms. In both chapters, Δ^9-tetrahydrocannabinol (THC) is used as a model drug that is both lipophilic and chemically labile. THC is a highly viscous and sticky resin and chemical degradation occurs rapidly when it is exposed to air. Therefore, THC is difficult to handle and a challenge to formulate

into a dosage form. In chapter 6, it is tested whether THC can be incorporated in inulin to obtain a dry material in which THC is stabilized. Furthermore, chapter 6 shows that a fast disintegrating tablet suitable for sublingual or oral application can be formulated starting from a solid dispersion composed of inulin glasses in which THC is incorporated. In chapter 7, a spray freeze drying process is developed to further improve the incorporation process of THC in inulin. The stability of THC is measured and compared with normal freeze drying. The particles obtained by spray freeze drying are characterized and tested for their suitability for dry powder inhalation.