

# Chapter 2

## Theoretical Considerations in Developing Amorphous Solid Dispersions

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### 2.1 Introduction

The term “solid dispersion” was introduced by Chiou and Riegelmann in 1971 who defined solid dispersions as “a dispersion of one or more active ingredients in an inert carrier at the solid state, prepared by either the melting, the solvent or the melting solvent method” (Chiou and Riegelman 1971). Although the concept of melting an active ingredient and carrier together had previously been used, Chiou and Riegelmann were the first to introduce a classification system for solid dispersions that was based on the possible physical states of the active pharmaceutical ingredient (API) and the carrier. Unfortunately, it is often found that the term “solid dispersion” is used somewhat inconsistently in the pharmaceutical literature; therefore, this first section briefly gives an overview over the nomenclature of different types of solid

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**Table 2.1** Classification of solid dispersions

| State of API | Number of phases |                  |
|--------------|------------------|------------------|
|              | 1                | 2                |
| Crystalline  | Solid solution   | Eutectic mixture |
| Amorphous    | Glass solution   | Glass suspension |

*API* active pharmaceutical ingredient

dispersions (Table 2.1). The number of components is not limited to two; however, in the following chapter, we restrict ourselves to binary systems, consisting of API and carrier. We use the term “solubility” to describe the solubility of the crystalline drug in the carrier and the term “miscibility” to describe the miscibility of the amorphous drug with the polymer.

The advantage of using solid dispersions as drug delivery systems to increase the dissolution behavior and apparent solubility of a drug is discussed in more detail later in this chapter. In brief, molecularly dispersing a poorly water-soluble API in a hydrophilic carrier (amorphous or crystalline) often leads to increased dissolution behavior and supersaturation of the drug when this system is exposed to water. This is attributed to a number of factors such as improved wettability of the drug by the polymer, minimal particle size of the drug, separation of individual drug particles by polymer particles, and subsequent prevention of drug precipitation upon contact with aqueous media.

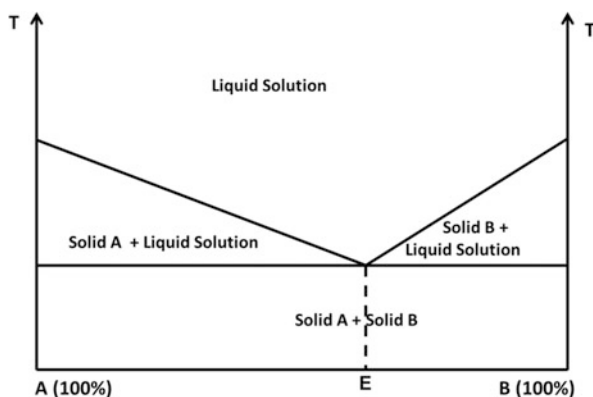
## 2.2 Classification of Solid Dispersions

### 2.2.1 Eutectic Mixtures

A simple eutectic mixture consists of two compounds that are completely miscible in the liquid state (melt) but only show limited miscibility in the solid state. At a specific composition (E in Fig. 2.1), the two components crystallize simultaneously when the temperature is reduced (Fig. 2.1). If mixtures with different compositions to the eutectic composition of A and B are cooled, one component will start to crystallize before the other, which initially leads to a mixture of pure solid compound and liquid. Therefore, a true eutectic only exists for a defined composition of A and B. The microstructure of a eutectic mixture is different from the microstructure of either components, and this property may be used to differentiate the eutectic mixture from other forms of crystalline mixtures. A theoretical method to determine the eutectic composition of a binary mixture and the temperature at which it crystallizes has been suggested by Karunakaran (1981).

Eutectics of poorly soluble compounds and water-soluble inert carriers have been shown to enhance the dissolution rate of the poorly soluble compound. When the eutectic is exposed to water or the gastrointestinal (GI) fluids, the carrier will dissolve

**Fig. 2.1** Phase diagram of a simple eutectic system



rapidly and release fine crystals of the drug. Through the large surface area and the improved wettability from the carrier, the dissolution rate of the API will be enhanced.

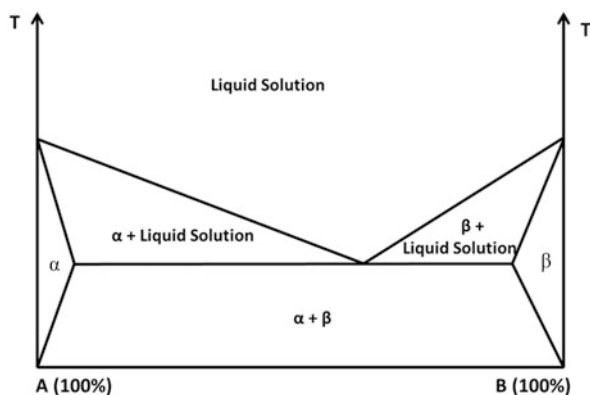
### 2.2.2 Solid Solutions

Solid solutions are formed when a solute is nonstoichiometrically incorporated into the crystal lattice of the solvent (Moore and Wildfong 2009). Solid solutions can be classified according to the solubility of the solute in the crystal lattice (continuous vs. discontinuous) or according to the way in which the solute molecules are distributed. In general, the term “solid solution” refers to systems that contain a crystalline carrier.

**Continuous Solid Solutions** In continuous solid solutions, the components are miscible in all proportions. This occurs if the strength of the bonds between the two different molecules is higher than that of the bonds of the molecules of the same species. Organic molecules do not tend to form this kind of solid solutions and therefore, they are not of great importance in the pharmaceutical field (Leuner and Dressman 2000).

**Discontinuous Solid Solutions** The term “discontinuous” refers to the fact that solid solubility only exists at specific compositions of the mixture, not over the entire compositional range. Figure 2.2 represents a phase diagram of a discontinuous solid solution. Each component is capable of completely dissolving the other component in a specific compositional region (regions  $\alpha$  and  $\beta$  in Fig. 2.2) whereby the solubilization capability of the components is temperature dependent. It is maximal at the eutectic temperature and decreases when the temperature is reduced (Leuner and Dressman 2000). In reality, limited solid solubility most likely exists for all, or at least very many, binary systems. Goldberg et al. (1965) therefore proposed to use the term “solid solution” only if the mutual solubility of the two components exceeds 5%. In their work, they could show that the postulated eutectic mixture of sulfathiazole in urea by Sekiguchi and Obi (1961), which was shown to increase the

**Fig. 2.2** Phase diagram of a discontinuous solid solution



drug absorption rate in man, should indeed be regarded as a physical mixture of two solid solutions.

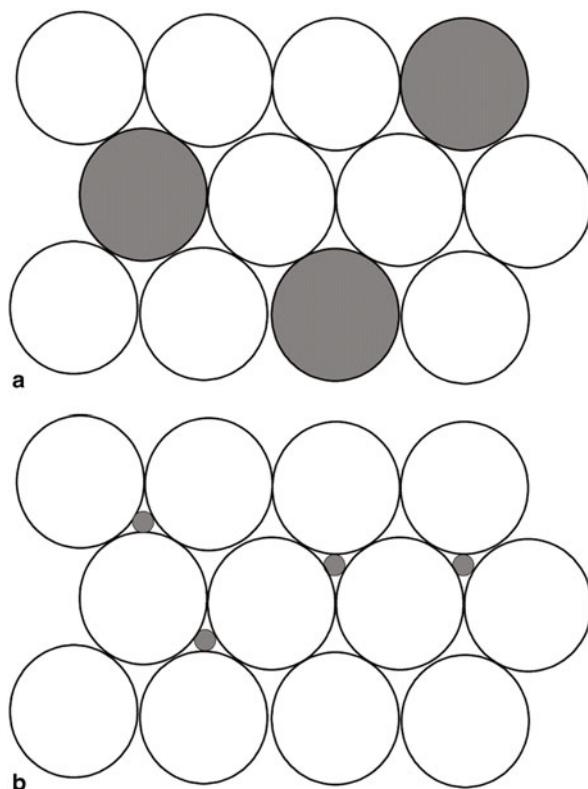
**Substitutional Solid Solutions** In typical solid solutions with a crystalline carrier, a solute molecule can substitute for a carrier molecule in the crystal lattice (illustrated in Fig. 2.3a). Substitution is only possible if the size of the solute molecule is approximately similar to the size of the carrier molecule. Substitutional solid solutions can be continuous or discontinuous.

**Interstitial Solid Solutions** If the solute molecules are smaller than the solvent molecules, it is possible for them to occupy the interstitial spaces in the crystalline lattice (illustrated in Fig. 2.3b). The diameter of the solute molecules should not exceed 0.59 times the diameter of the solvent. Interstitial solid solutions can only form solid solutions of the discontinuous type (Khachaturyan 1978).

### 2.2.3 Glass Solutions

In glass solutions, the carrier is amorphous and the solute molecules are dispersed molecularly in the amorphous carrier. Glass solutions therefore are homogeneous one-phase systems. However, due to the much higher viscosity of glass solutions compared to liquid solutions, the distribution of solute molecules in the carrier may be irregular and a homogeneous distribution within the glass solution needs to be ensured by mixing. Chiou and Riegelmann (1969) formulated a glass solution of griseofulvin in citric acid to improve the dissolution rate of griseofulvin. In the past, sugars and urea were used as amorphous carriers, but more recently, organic polymers such as poly(vinylpyrrolidone) (PVP) and cellulose derivatives are commonly used. These polymers often exhibit amorphous regions (or are fully amorphous) and can be tailor-made for specific purposes. If the solubility of the drug in the carrier is not exceeded, the glass solution is thermodynamically stable. However, the concentration of the solute is often supersaturated to achieve higher drug loads and

**Fig. 2.3** **a** Substitutional crystalline solid solution and **b** interstitial crystalline solid solution

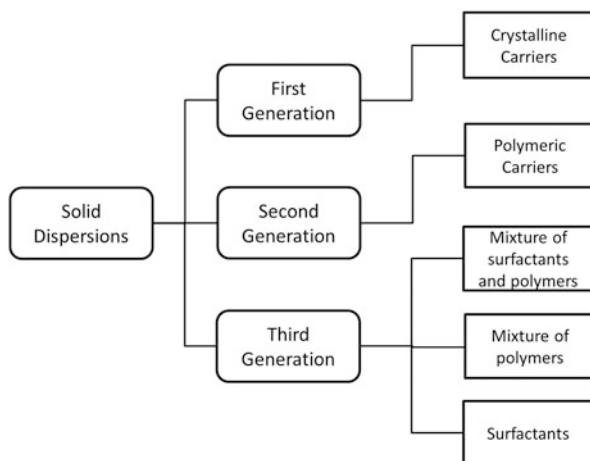


therefore recrystallization and precipitation may occur. Recrystallization may be retarded by kinetic stabilization. Phase separation, as the first step to recrystallization, requires a certain degree of molecular mobility within the system, and storing glass solutions at temperatures well below the glass transition temperature ( $T_g$ ) will slow down mobility and may increase the stability of supersaturated glass solutions.

#### 2.2.4 *Glass Suspensions*

As stated above, it is often observed that the miscibility of an amorphous drug in an amorphous carrier is limited, and as the drug content increases, phase separation can occur. If the drug forms a separate amorphous phase (or a drug-rich amorphous phase), the glass solution has been converted to a glass suspension. In this form, the drug is still present in the amorphous form, so it will still show increased dissolution behavior compared to the crystalline form; however, these amorphous precipitates have a high likelihood for recrystallization of the amorphous drug (usually the  $T_g$  of the drug or drug-rich phase will be lower than the  $T_g$  of the polymer or polymer-rich phase).

**Fig. 2.4** Classification of solid dispersions. (Adapted from Vasconcelos et al. 2007)



Recently, a number of publications have presented a classification scheme of solid dispersions which is not based on the molecular structure but rather based on the advancement of knowledge and complexity of these systems. The authors categorize solid dispersions as first-, second-, and third-generation solid dispersions (Vasconcelos et al. 2007). This classification can be regarded as a kind of timeline showing the evolution of solid dispersion development and their increasing complexity as drug delivery systems (Fig. 2.4). This chapter predominantly covers second-generation solid dispersions.

## 2.3 Theoretical Considerations Regarding Solid Dispersions

### 2.3.1 Solubility Advantage of the Amorphous Form

Amorphous forms show excess free energy, enthalpy, and entropy compared to the corresponding crystalline state(s) and therefore their solubility in the GI tract may be higher, which results in potentially higher bioavailability of the drug.

However, before pursuing the laborious route of amorphous formulation development, the formulation scientist would benefit from a priori knowledge of whether the amorphous route is viable and how much solubility improvement, and hence potential increase in bioavailability, can be expected. For a crystalline material, simple solubility measurements and (intrinsic) dissolution testing are the most common methods for comparing solubility. Solubility and dissolution testing of amorphous compounds, however, is not as straightforward, and there are numerous reports in the literature on the difficulties associated with solubility and dissolution rate determination of an amorphous form, as amorphous material tends to recrystallize upon contact with the dissolution media (Alonzo et al. 2010; Babu and Nangia 2011; Egawa et al. 1992; Greco and Bogner 2010; Imaizumi et al. 1980).

For different polymorphs, the solubility advantage of one polymorph over the other can easily be calculated using the thermodynamic parameters of each polymorph. In a method proposed by Parks et al. (1928; 1934), the solubility difference between different polymorphs is estimated using the solubility ratio,  $\sigma^1/\sigma^2$ . The solubility ratio is directly related to the free energy difference,  $\Delta G^{1,2}$ , between polymorphs 1 and 2:

$$\Delta G_T^{1,2} = -RT \ln (\sigma_T^1 / \sigma_T^2), \quad (2.1)$$

where  $\Delta G_T^{1,2}$  is the free energy difference between polymorphs 1 and 2 at any given temperature ( $T$ ) and  $R$  is the gas constant. The difference in free energy can be estimated from the enthalpy ( $\Delta H$ ) and entropy ( $\Delta S$ ) differences of both forms:

$$\Delta G_T^{1,2} = \Delta H_T^{1,2} - (T \Delta S_T^{1,2}). \quad (2.2)$$

For crystalline compounds, the calculated solubility ratio gives accurate results. It has therefore been proposed to apply this equation to amorphous systems:

$$\Delta G_T^{a,c} = \Delta H_T^{a,c} - (T \Delta S_T^{a,c}) \quad (2.3)$$

whereby the entropy and enthalpy differences can be calculated from the entropy and enthalpy of fusion and the heat capacities ( $C_p$ ):

$$\Delta H_T^{a,c} = \Delta H_f^c - (C_p^a - C_p^c)(T_f^c - T) \quad (2.4)$$

$$\Delta S_T^{a,c} = \Delta S_f^c - (C_p^a - C_p^c)(\ln T_f^c - T) \quad (2.5)$$

$$\Delta S_f^c = \Delta H_f^c / T_f^c. \quad (2.6)$$

In this simplified approach, the amorphous form is treated as a pseudo-equilibrium state. Solubility advantages calculated by this method have predicted solubility advantages of up to 1600-fold for amorphous systems compared to their crystalline counterparts (Graeser et al. 2010; Hancock and Parks 2000). When compared to experimentally determined solubility data, the observed increase in solubility, however, was considerably lower. In the past, this has always been attributed to the difficulty in measuring the solubility of amorphous systems in aqueous media due to recrystallization and the nonequilibrium nature of the amorphous form (Egawa et al. 1992; Imaizumi et al. 1980). In a recent publication, however, some shortcomings of the proposed simplified calculations were highlighted. It was postulated that the large discrepancies between the theoretical and experimentally determined solubility increase can be attributed to inaccurate assumptions regarding the  $C_p$  differences, changes in the amorphous free energy due to water sorption, and a reduced fraction ionized in saturated solutions of the amorphous form (Murdande et al. 2010a). By including correction terms for these three considerations, the authors were able to calculate the solubility advantage for amorphous indomethacin to be 7-fold instead of the previously determined 25–104-fold higher solubility, compared to the crystalline form of the drug. This was in closer agreement to the experimentally observed

value of 4.9. In a second study, the authors reported that the calculated and observed solubility advantages were in agreement only if recrystallization in the medium was slow (Murdande et al. 2010b). This limitation highlights once again the difficulties in determining the solubility and dissolution behavior of amorphous compounds.

Determination of the solubility advantage using this modified method, however, gives useful estimates of the expected solubility increase and can thus serve as a basis to decide whether the amorphous route should be pursued in development of a specific poorly water-soluble drug. Only drugs for which the solubility increase is considered sufficient should be selected for further testing and development.

### ***2.3.2 Glass-Forming Ability (GFA) and Glass Stability (GS)***

Research over the past decades has shown that different crystalline drugs have different tendencies to be converted into and remain in the amorphous form. Although several technologies exist to convert a crystalline drug into the amorphous form, but in practice, not every drug is susceptible to amorphization. Thermolabile drugs may not be transformed using heat-based methods, while poor solubility in organic solvents may prevent the use of spray drying or precipitation methods. Additionally, drugs that show a poor tendency to amorphization regardless of the technology used exist.

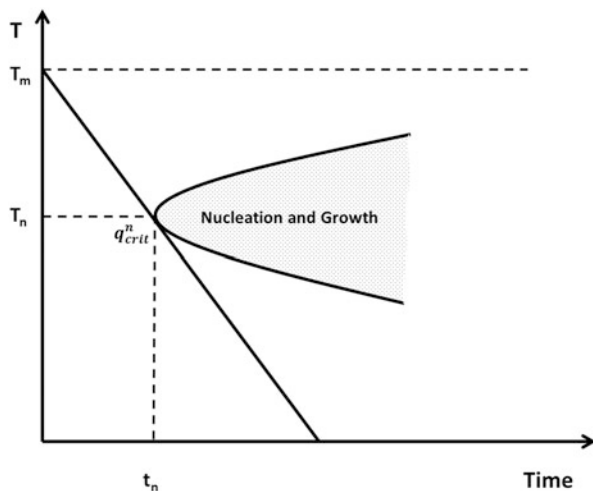
To assess whether a compound is capable of being developed into an amorphous dosage form, the glass-forming ability (GFA) of the drug can be estimated. The GFA has been defined as the ease of vitrification of a liquid upon cooling, and there is no shortage of structural and kinetic theories behind it (Avramov et al. 2003). Once successfully converted to the amorphous form, drugs may exhibit different tendencies to revert back to the energetically favored crystalline state. This recrystallization process may occur in a time frame of several seconds up to several years, depending on the drug used and the conditions at which it is stored.

Whereas the GFA describes the ease of vitrification of a compound, the glass stability (GS) describes its resistance to recrystallization. In the past decades, researchers not only in the pharmaceutical field but also in the field of inorganic chemistry have investigated the GFA and GS of numerous glasses. However, despite such research, the fundamental understanding, and thus prediction models, of the recrystallization process is still lacking. For the pharmaceutical scientist, prediction models for the GFA and GS would be of great benefit, as real-time preparation and storage experiments would potentially become redundant. This would be a time- and cost-saving improvement in the development process for new drugs.

After assessing whether a poorly soluble drug would benefit from being formulated in the amorphous form in terms of solubility increase, the GFA should be the subsequent property to determine. The most common parameter to estimate the GFA of a compound is to assess its minimum cooling rate, i.e., the slowest cooling rate from the melt at which the material can still be transformed to the amorphous form. Drugs which show poor GFA are thought to exhibit a high degree of mobility in



**Fig. 2.5** Annotated time–temperature transformation diagram, showing the minimum cooling rate to avoid crystallization.  $T_m$  is the melting temperature,  $T_g$  is the glass transition temperature, and  $T_n$  and  $t_n$  are the temperature and time point at the locus, respectively. (Adapted from Karmwar et al. 2011a)



the melt, so that the melt can only solidify to an amorphous form if the temperature change (cooling rate) is sufficiently rapid. In contrast, the amorphous form can be attained by slow cooling rates for drugs with high GFA.

This critical cooling rate ( $q_{crit}^n$ ) has been estimated by use of isothermal time–temperature transformation (TTT) diagrams (Uhlmann 1972) or continuous cooling transformation (CT) curves Onorato and Uhlmann 1976).

Applying the TTT method, the critical cooling rate is given by Eq. 2.7:

$$q_{crit}^n = \frac{T_m - T_n}{t_n} \quad (2.7)$$

whereby  $T_m$  is the melting temperature and  $T_n$  and  $t_n$  are the minimum temperature and time where an amorphous form can still be achieved (Fig. 2.5).

However, it has been discussed that the critical cooling rate calculated by the TTT method often differs by up to one order of magnitude from the experimentally determined values (Huang et al. 1986). As the measurement of  $q_{crit}^n$  is time and material consuming and the measurements are often not straightforward, a variety of thermal observations have been proposed as surrogates for the critical cooling rate such as, the melting temperature  $T_m$ , the glass transition temperature  $T_g$ , the crystallization temperature  $T_c$ , and combinations thereof. These thermal events can easily be obtained by differential scanning calorimetry (DSC) measurements. Barandiaran and Colmenero (1981) were among the first to develop a DSC-based method in which the crystallization temperature is determined while a liquid is being cooled in a DSC instrument at different rates, and they established the following relationship (Eq. 2.8), which was later refined to Eq. 2.10 (Cabral et al. 2003):

$$\ln q = A - \frac{B}{(\Delta T_c^c)^2} \quad (2.8)$$

$$\Delta G(T_c^c) = S_m \Delta T_c^c \quad (2.9)$$

$$q_{\text{crit}}^{\text{n}} = \exp \left( A - \frac{B}{T_{\text{m}}^2} \right), \quad (2.10)$$

where  $q$  is the cooling rate,  $A$  and  $B$  are empirical constants obtained from linear regression,  $T_{\text{c}}^{\text{c}}$  is the crystallization peak temperature on cooling, and  $\Delta T_{\text{c}}^{\text{c}}$  is the difference between  $T_{\text{m}}$  and  $T_{\text{c}}^{\text{c}}$ . In essence, the equation states that compounds which have a low thermodynamic driving force for recrystallization,  $\Delta G(T_{\text{c}}^{\text{c}})$ , and high melting entropy ( $S_{\text{m}}$ ) should be good glass formers (Eq. 2.9). Only few researchers have calculated the minimum cooling rate using this method; however, the calculated and experimentally determined values agreed (Whichard and Day 1984). A number of other researchers have investigated and proposed alternative methods for calculating the critical cooling rate, making small alterations to already existing equations. These different approaches are beyond the scope of this chapter and the interested reader is referred to the literature for further details (Gutzow and Schmelzer 2013; Whichard and Day 1984).

The concept of the GFA was developed for inorganic materials, and studies on the estimation of the GFA through measurement of the critical cooling rate for small organic molecules are scarce. For pharmaceutically relevant systems, DSC-based methods are of particular interest as they offer a rapid and simple way of estimating the GFA of an unknown drug. These methods use the thermal events from heating experiments in a DSC to assess the GFA. In the 1940s, Kauzmann introduced a ratio which was later termed the reduced glass transition temperature ( $K_{\text{T}}$ ) by Turnbull (Kauzmann 1948; Turnbull 1969).

$$K_{\text{T}} = \frac{T_{\text{g}}}{T_{\text{m}}} \quad (2.11)$$

with  $T_{\text{m}}$  being the melting temperature and  $T_{\text{g}}$  the glass transition temperature.  $K_{\text{T}}$  is considered a predictor for the resistance to crystallization. The higher the value of  $K_{\text{T}}$ , the higher the GFA should be. The theory behind this simple equation relies on the assumption that the viscosity of compounds is equal at  $T_{\text{g}}$  and therefore materials with a higher value for  $K_{\text{T}}$  are expected to have a higher viscosity between  $T_{\text{g}}$  and  $T_{\text{m}}$ . Hence, the closer the value of  $K_{\text{T}}$  is to 1, the higher is the GFA of the compound.

Weinberg (1994) used an approach in which not only the  $T_{\text{g}}$  but the difference between  $T_{\text{g}}$  and the crystallization temperature was used to estimate the GS. It is assumed that larger differences between these two temperatures reflect a higher GFA:

$$K_{\text{W}} = \frac{T_{\text{x}}^{\text{h}} - T_{\text{g}}}{T_{\text{m}}}, \quad (2.12)$$

where  $K_{\text{W}}$  is the “Weinberg parameter” and  $T_{\text{x}}^{\text{h}}$  is the crystallization onset temperature.

In the past, there has been no shortage of authors and equations, all intending to establish the optimal equation in order to estimate the GFA of a drug (Eqs. 2.13, 2.14

Amorphous Solid Dispersions

Theory and Practice

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