ZURÜCK

Poster

Thermoanalytical Investigations of Crystalline and Amorphous Forms of a Drug Candidate

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1. Introduction

A drug candidate compound exists in a crystalline and an amorphous form. The possibility of polymorphic or pseudopolymorphic forms was tested by a crystallization screening in various solvents. The drug candidate was crystallized from different solvents (water, methanol, ethanol, 1-butanol, tetrahydrofuran, diethyl ether, acetone, acetonitrile, n-heptane and xylene). The resulting crystals from the recrystallization and from the mother liquor were obtained always as the same crystal form. Precipitation from the free base by methane sulfonic acid in acetone/water gives also the same crystal form. The drug candidate exists only in one crystal modification. This crystalline form shows a poor solubility. A metastable amorphous form was tested to increase the dissolution rate and bioavailability. The amorphous form was obtained by lyophilisation. Since the amorphous state is thermodynamic instable compared to the crystalline state it was necessary to check the stability of the amorphous state under storage or manufacturing conditions.

2. Experimental

A commercial Thermal Analysis System with 2910 MDSC, 910 DSC, and 2950 High Resolution TGA modules (TA Instruments) was used for all measurements. The storage of the samples at different levels of relative humidity was carried out in closed boxes over defined salt solutions /1/. The melting process of the crystalline form and the cold crystallisation of the amorphous form was observed with polarized microscope (Bausch & Lomb) combined with a hot stage (Reichert & Jung).

3 . Results

A) Melting behaviour of the crystalline form

The melting behaviour of the crystalline form was investigated by DSC, TG and hot stage microscopy. A typical melting was observed in the hot stage microscopy investigation. A heating rate dependence on the observed melting point was found by DSC and thermomicroscopy. A mass loss was not detected in the equivalent temperature range. The higher the heating rate, the higher the observed melting point is (figure 1 and table 1).

The reason for the decrease of the melting point is the formation of an impurity by decomposition depending on the heating time, which increases with decreasing heating rate. The determination of the melting point of the pure compound should possible by extrapolation to infinite high heating rates. A simple reciprocal temperature - logarithmic heating rate graph is non-linear. The melting point depression by impurities is able to describe by the Schröder-van-Laar equation. The formation of the impurity depends on the heating rate. A combination of the Schröder-van-Laar equation and a first order decomposition model was used for the calculation.

Table 1

Heating rate β (K/min)	Melting Point (°C)	Melting enthalpie (J/g)
1	270.8	149.0
2	274.6	149.0
5	279.0	152.2
10	281.2	149.5
20	283.5	148.8
50	285.1	140.0

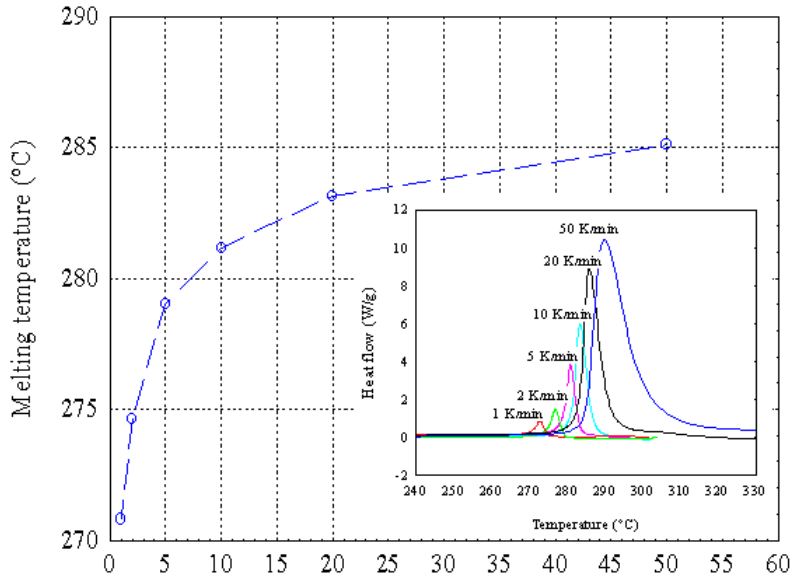

Figure 1

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Schröder-van-Laar equation

$$\frac{1}{T} = \frac{1}{T_f} - \frac{R}{\Delta_f H} \cdot \ln x$$

$$\ln x = \frac{\Delta_f H}{R}\left(\frac{1}{T_f} - \frac{1}{T}\right)$$

First-order decomposition

$$\frac{d\alpha}{dt} = A \cdot e^{-\frac{E_A}{RT}} \cdot f(\alpha) \quad \text{with} \quad f(\alpha) = 1 - \alpha$$

$$\frac{d\alpha}{dT} = \frac{A}{\beta} \cdot e^{-\frac{E_A}{RT}} \cdot (1 - \alpha)$$

$$\int_0^{\alpha} \frac{d\alpha}{1-\alpha} = \frac{A}{\beta}\int_{T_0}^{T} e^{-\frac{E_A}{RT}} dT$$

$x = 1 - \alpha$

Doyle's approximation

$$\ln x = \frac{E_A A}{R\beta}\left(-5.3305 + 1.052\frac{E_A}{R}\frac{1}{T}\right)$$

$$\frac{1}{T} = \frac{\frac{1}{T_f} + 5.3305 \cdot \frac{E_A R}{\Delta_f H}\frac{1}{\beta}}{1 + 1.052\frac{E_A^2 A}{R\Delta_f H}\frac{1}{\beta}} \longrightarrow \boxed{\frac{1}{T} = \frac{a_1 + a_2\frac{1}{\beta}}{1 + a_3\frac{1}{\beta}} \quad with \quad a_1 = \frac{1}{T_f}}$$

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The extrapolated melting point is the result from a non-linear regression of a reciprocal temperature to reciprocal heating rate function (figure 2). The method is able to be used for a better comparison of polymorphs which partly decompose during heating.

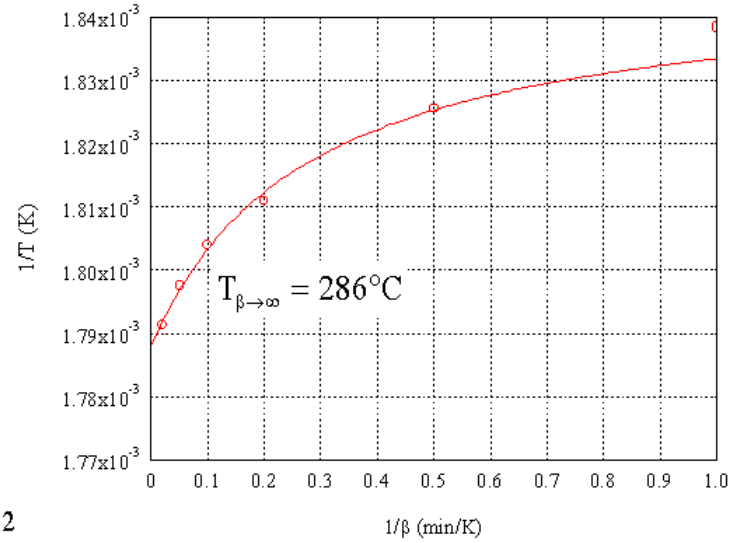

Figure 2

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B) Characterization of the amorphous form

B.1) Thermoanalytical measurements

DSC measurements shows the typical course for amorphous substances (figure 3). First the glass transition combined with an enthalpy relaxation is observed. During further heating the exothermic cold crystallization takes place. At last the crystallized material melts. The cold crystallisation is able to observe by thermomicroscopy too. The formation of light spots indicates the start of cold crystallization by use of polarized light. The method is also usable to check the amorphous materials for crystalline seeds. During the investigation of different batches of amorphous material a variation of glass transition temperatures and cold crystallization temperatures was detected. An investigation of the effects of humidity, storage time and heating rate was carried out for a better interpretation of this variations. The fragility /2, 3/ and the Kauzmann temperature was determined for a stability estimation of the amorphous state.

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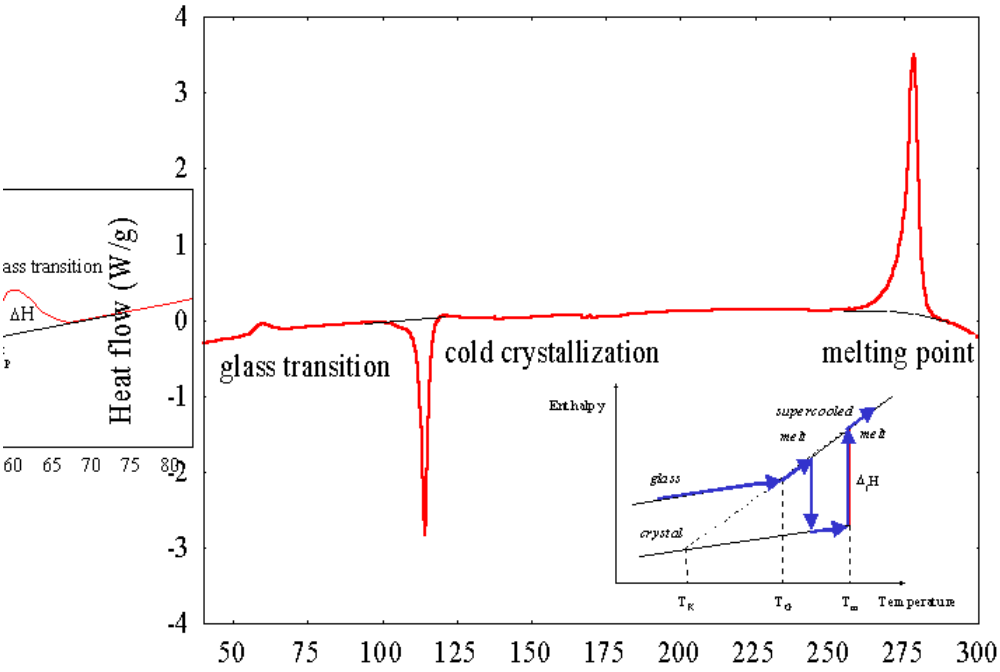

Figure 3

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B.2) Effect of relative humidity

Samples of the drug candidate were stored at different levels of relative humidity over one, two or three days. After storage a decrease of the glass transition temperatures and cold crystallization temperatures with increasing humidity was found (figure 4). A significant change of the glass transition from 65°C to 50°C and of the cold crystallisation from 105°C to 80°C took place. Analogous thermogravimetric measurements shown that no additional water was absorbed in dependence on the humidity. At 63 % RH a complete crystallization of the amorphous materials was detected within one day at room temperature. A extrapolation of the glass transition course to this humidity level gives approximately 40°C. The crystallization seems to proceed below the glass transition. A similar behaviour was found by other lyophilized formulations by the measurement of glass transition temperatures and NMR relaxation-based critical mobility temperatures /4/. In view of the stability of the amorphous materials a storage at low levels of relative humidity is necessary.

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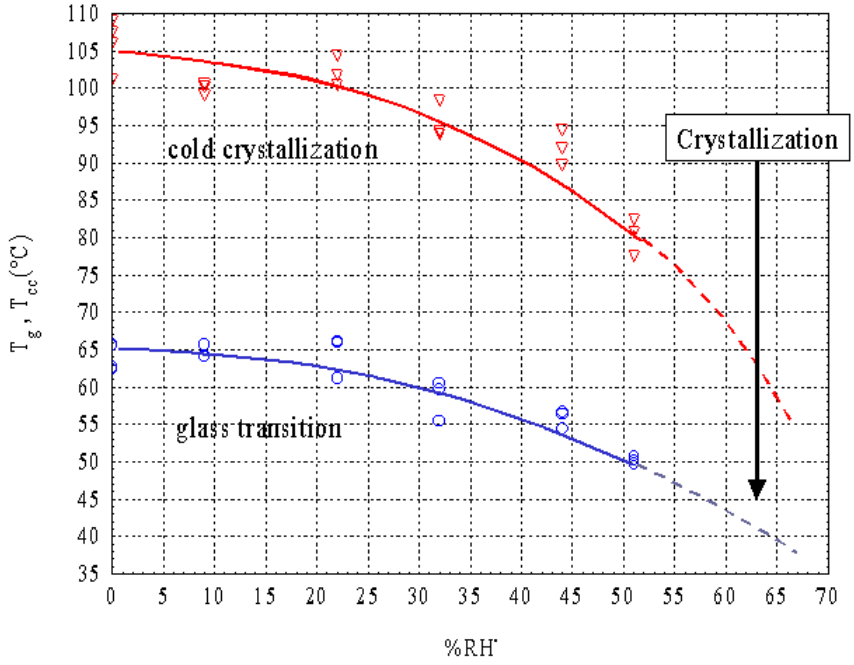
Figure 4



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B.3) Effect of storage time

The lyophilisates have shown a shift of the glass transition and cold crystallisation to higher temperatures during storage at room temperature. In the same way the enthalpy relaxation increases during the storage. The figures 5 and 6 show this behaviour for different lyophilisate batches. The material seems to undergo a stabilisation during storage at room temperature.

Figure 5

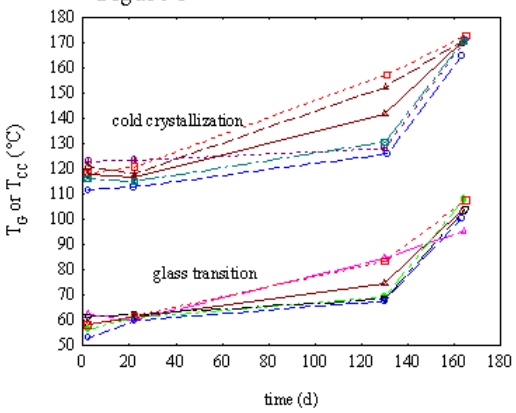
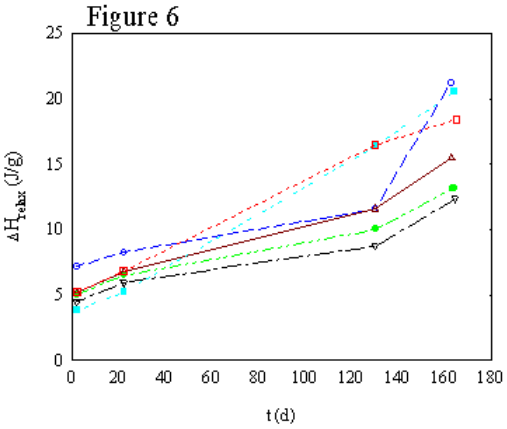


Figure 6



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B.4) Determination of the fragility and the Kauzmann temperature

The stability of the amorphous state is estimated on the one hand by the so-called fragility parameter /2, 5/ and on the other hand by the Kauzmann temperature /6, 7/. Fragility m is defined as:

$$m = \frac{E_A}{2.303 \cdot R \cdot T_g}$$

E_A - apparent activation energy for molecular motions at T_g

The fragility describes the stability from kinetic view. The apparent activation energy was determined by investigation of the dependence of the glass transition on the heating rate (Ozawa-Flynn method, figure 7). The resulting fragility parameter 15 indicates a stable amorphous state.

The Kauzmann temperature describes the stability more from thermodynamic view as the temperature at which the enthalpies of the supercooled melt and the crystalline state are equal. The theoretical Kauzmann temperature T_K represents a conservative stability limit for amorphous forms. The estimation succeeds by the analysis of enthalpy differences between the crystalline state and the melt or supercooled melt at different temperatures /6/. Figure 8 shows the plot of all cold crystallizations measured under different conditions (%RH, storage, heating rate) and the extrapolated melting point. A linear regression gives the Kauzmann temperature of T_K = -36°C.

Figure 7

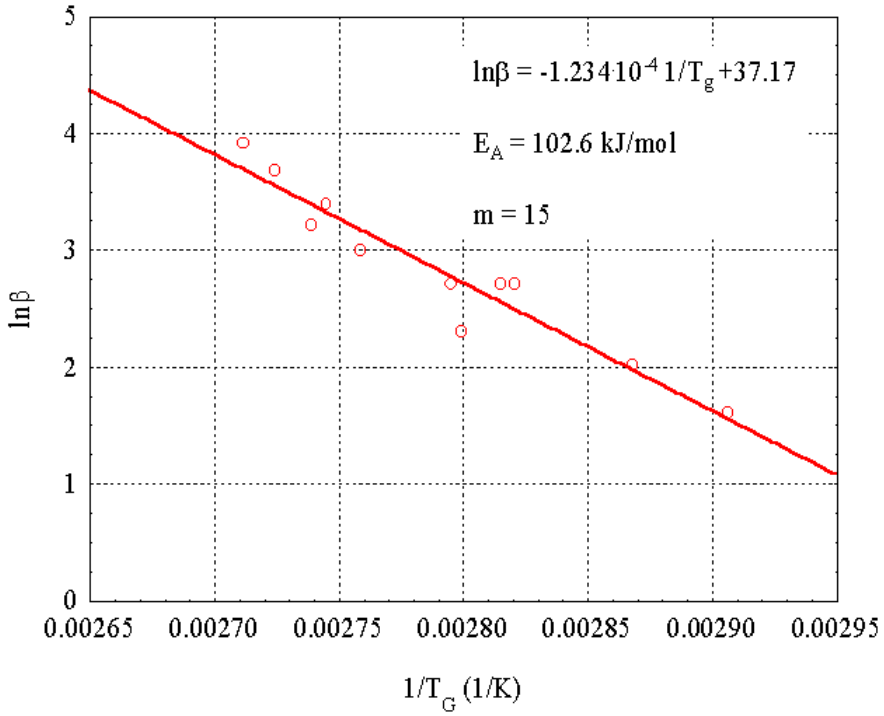
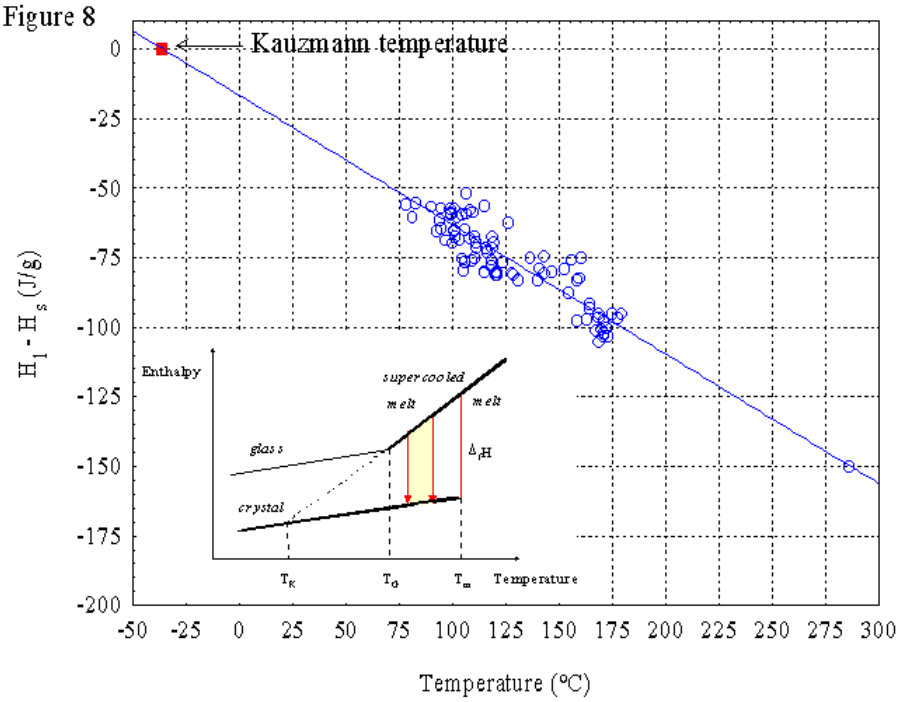


Figure 8



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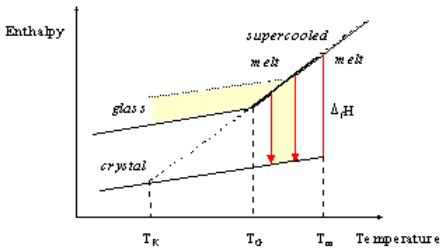
Conclusion

The amorphous state of the drug candidate is influenced by relative humidity. Water acts as plasticizer and increases the crystallization tendency. During storage at room temperature the increase of glass transition and cold crystallisation temperatures indicates a stabilisation of the materials. The stability of the amorphous state is given by kinetic reasons. The small value of fragility is a sign of an non-fragile or strong glass former. The thermodynamic limit with a Kauzmann temperature of -36°C is not practically usable. In sum it is necessary to avoid conditions which favour a cold crystallization. The Kauzmann plot is an additional confirmation for the extrapolated melting point.



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