Evaluation of thermodynamic and kinetic parameters as predictors of physical stability of the amorphous state

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Abstract summary

The aim of this study was to evaluate commonly calculated parameters of the amorphous state in terms of their predictive capabilities of physical stability.

Introduction

The main challenge in working with the amorphous form of drugs is their physical instability. In order to benefit from the advantages of enhanced solubility of the amorphous form, methods of stabilizing the amorphous state against recrystallization need to be found and optimized.
The stability of drugs is usually assessed by conducting time-consuming storage experiments such as physical stability studies under various conditions for each compound of interest. However, accelerated stability testing at high temperatures and humidity may not reflect the true stability behaviour of amorphous materials stored below their glass transition temperature (T_g) and experiments have to be carried out for each compound individually. There exists a so far unmet need for assessing the amorphous stability of any amorphous compound without requiring storage experiments.
Thermodynamic and kinetic parameters of the amorphous state have recently gained interest and were successfully correlated to the stability of the amorphous state[1,2]. However, this attempt was only applied to a limited number of compounds and a systematic approach for a greater sample size is currently lacking. Thus general conclusions are difficult to draw.
This study was intended to evaluate the potential of the thermodynamic and kinetic parameters as predictors of amorphous stability for a larger sample size.
In this study, the kinetic parameters relaxation time, τ, and the strength parameter, D, were assessed on the basis of the heating rate dependence of the glass transition temperature, T_g. The Adam-Gibbs equation was used to calculate the respective values.
The configurational thermodynamic parameters can be calculated from heat capacity measurements of the crystalline and the amorphous state by applying the method proposed by Zhou et al[3]. The thermodynamic factors were assessed for the temperature range above T_g.

Experimental methods

Materials

A sample size of 13 drugs with different physical (high and low T_g) and chemical (acidic, basic and neutral) properties was used:
acetaminophen, cefuroxime axetil, donepezil HCl, DRUG A, DRUG B, griseofulvin, indomethacin, lacidipine, nifedipine, salsalate, simvastatin, tolbutamide and troglitazone.

Determination of thermodynamic factors

Configurational heat capacity: Amorphous samples were prepared by heating and quench-cooling in the DSC (TA Instruments Q1000) and were measured immediately. Samples were heated at 1 K/min from 50 ºC below to 30 ºC above T_g. A modulation period of 100 s and amplitude of ± 0.5 K was applied. The configurational heat capacity (Cp_{conf}) was calculated as the difference between the heat capacities of the amorphous and the crystalline state and the configurational thermodynamic properties entropy (S_{conf}), enthalpy (H_{conf}) and Gibbs free energy (G_{conf}) were then calculated by applying the thermodynamic relationships outlined by Zhou et al[3].

Determination of kinetic factors

Scanning rate dependence of Tg: Amorphous samples were prepared by heating and quench-cooling in the DSC. After amorphization, the samples were heated twice in the instrument to a temperature 30 ºC above T_g and the second heating run was used for measurement of the T_g (mid-point). Heating (and cooling) rates employed were: 1, 2, 5, 10 and 20 K/min. Relaxation times were the calculated using a modified version of the Adam-Gibbs equation[4]. Fragility values were also calculated from this equation.

Stability storage

Drugs were melted on a hotplate and quench-cooled using liquid nitrogen. Drugs were stored under dry conditions at a temperature approximately 20 ºC below their respective glass transition temperatures (Table 1) for a duration of 3 months.

Table 1. Storage conditions of drugs, T_g – 20 ºC.

Drug	Tg [ºC]	Tg-20 [ºC]	storage conditions
tolbutamide	5	-15	freezer
salsalate	9	-9	freezer
acetaminophen	24	4	fridge
simvastatin	32	12	fridge
nifedipine	46	26	room temperature
indomethacin	46	26	room temperature
lacidipine	52	32	oven 30 °C
troglitazone	63	43	oven 40 °C
DRUG A	66	46	oven 40 °C
DRUG B	76	56	oven 60 °C
cefuroxime axetil	81	61	oven 60 °C
griseofulvin	90	70	oven 70 °C
donepezil HCl	98	78	oven 70 °C

Stability above T_g

Drugs were heated in the DSC and stability order of the drugs above T_g was determined by relating the recrystallization temperature, T_c, to T_g and the melting temperature, T_m via $(T_c-T_g) / (T_m-T_g)$ to give the reduced recrystallization temperature, which can be used to compare the stability of drugs with different T_gs. No recrystallization was taken as the most stable behaviour.

Results and Discussion

The calculated strength parameter D classified the drugs as being overall 'fragile' glass formers[5].

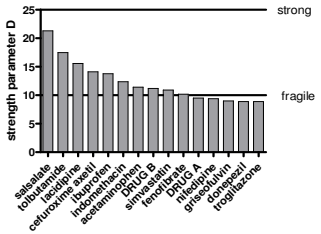

Figure 1. Fragility of drugs.

It can be seen that values for fragility span from 8.9 to 21.3 (Fig. 1). Therefore although these drugs are all classified as being 'fragile', there may be differences in their behaviour based on the differences in their degree of fragility.
Correlation of fragility with the actual stability from storage experiments gave an r^2-value of 0.227, indicating that a direct relationship between amorphous stability and fragility could not be established. However, it appears that 'strong' glass formers form a more stable amorphous state (cefuroxime axetil, salsalate, tolbutamide).
The results from the storage experiments showed that the drugs exhibited different stabilities when stored at T_g – 20 ºC (Fig. 2).

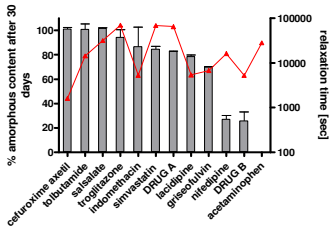

Figure 2. Relaxation time and amorphous content after 30 days.

After 30 days, cefuroxime axetil, salsalate and tolbutamide showed 100 % amorphous content while acetaminophen had recrystallized completely. No direct linear correlation was found between the calculated relaxation times and the stability of the amorphous forms (r^2 <0.04).
The configurational thermodynamic parameters S_{conf}, H_{conf} and G_{conf} were correlated to the stability above the T_g (Fig. 3).

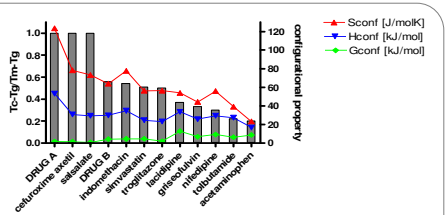

Figure 3. Configurational thermodynamic properties and stability of drugs above T_g.

The r^2 – values showed that some correlation exists between S_{conf} and the stability of the amorphous state above T_g (Table 2).

Table 2. Linear regression parameter r^2 for configurational thermodynamic properties.

	S_{conf}	H_{conf}	G_{conf}
r^2	0.685	0.343	0.568

Conclusions

All drugs were calculated as 'fragile' glass formers, however, variation in the degree of fragility within this group was highlighted. Below the T_g, fragility showed no linear correlation with amorphous stability, although an indication exists that 'strong' glass formers may form more stable glasses. It could be shown that below T_g no clear relationship between the various factors and physical stability exists, indicating that stability predictions on the basis of relaxation time or fragility alone, as has been done in the past[6,7], may be inadequate. However, through appropriate assessment of parameters for a number of compounds, potential parameters for input into future multivariate analysis have been identified.
Above T_g, S_{conf} showed the largest correlation with stability. However, the stability above T_g cannot necessarily be related to the stability below T_g and therefore S_{conf} may only serve as a limited predictor of stability.

References

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Acknowledgements

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