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Evaluation of different calorimetric methods to determine the glass transition temperature and molecular mobility below T_g for amorphous drugs

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Abstract

The purpose of the present study was to compare different calorimetric methods used to determine the glass transition temperature (T_g) and to evaluate the relaxation behaviour and hence the stability of amorphous drugs below their T_g. Data showed that the values of the activation energy for the transition of a glass to its super-cooled liquid state qualitatively correlate with the values of the mean molecular relaxation time constant of ketoconazole, itraconazole and miconazole, three structurally related drugs. Estimation of the molecular mobility by activation energy calculation indicated that loperamide was more stable than its two building blocks T263 and R731. It was further shown that the most commonly used approach to determine T_g ($T_{g\,1/2c_p}$) leads to erroneous values when enthalpy recovery is significant. In this case, an alternative method based on enthalpic considerations leads to results in accordance to basic thermodynamics. Estimation of molecular mobility based on activation energy calculations is therefore considered to be a valuable alternative for the method based on measurement of the extent of relaxation. When enthalpy relaxation is important, the use of $T_{g\,1/2c_p}$ leads to an overestimation of the T_g.

Keywords: Differential scanning calorimetry; Molecular mobility; Amorphous drugs; Azole derivates; Loperamide

1. Introduction

The formulation of solid dispersions has been the focus of increasing interest during the last decades since such a dosage form might overcome dissolution rate limited oral absorption. In these dispersions the drug is often present as an amorphous or partially amorphous substance. Although the amorphous state is a high-energy state resulting in enhanced dissolution rate, from a thermodynamic point of view it is a metastable state and devitrification will eventually take place. If however, the time scale of devitrification and crystallization is very large, the dispersions can be stored for a long time without any risk for these phenomena to occur. It is therefore important to characterize the glassy drug as such and especially its stability during or before the formulation of solid dispersions.

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The main objective of this report is to compare two calorimetric methods that can be used to study the relaxation behaviour of glassy materials below their glass transition temperature (T_g). In order to assess a qualitative correlation between the two methods, three structurally related drugs (itraconazole, ketoconazole and miconazole) were used as model drugs. The first method is based on the estimation of the mean molecular relaxation time constant (τ). In this procedure, the extent of relaxation based on enthalpy recovery measurements by DSC, is being fitted to the Williams–Watts decay function, from which the mean molecular relaxation time constant at different temperatures below T_g can be calculated (Williams and Watts, 1970; Hancock et al., 1995; Van den Mooter et al., 1999; Shamblin et al., 1999; Di Martino et al., 2000; Van den Mooter et al., 2001; Six et al., 2001).

The second method involves the investigation of the influence of the applied heating rate on the observed glass transition temperature in a standard DSC-experiment. Based upon the following equation derived by Barton, the activation energy (E_a) for the transition from the glassy to the super-cooled liquid state can be calculated (Barton, 1969):

$$\ln q_+ = -\frac{E_a}{RT}$$

In this equation q_+ represents the heating rate, R is the universal gas constant and T the T_g measured at the heating rate q_+.

The first part of the paper, emphasizes on the determination of the T_g of small organic molecules. Since in a DSC-curve, devitrification does not appear as a sharp transition but takes place over a certain temperature interval, one can determine the T_g based upon several methods. From these the most commonly used in the pharmaceutical field is the temperature at half the height of the shift in the heat flow signal ($T_{g\,1/2c_p}$). Other options are to use the extrapolated onset temperature or the temperature corresponding to the inflection point. Another method which was described by Richardson (T_{gr}) and which is already known in polymer science, is based on enthalpic considerations (Richardson, 1994). It will be shown that this method leads to more accurate values of T_g, not only in the case of polymers but also for small organic molecules.

2. Materials and methods

2.1. Materials

Two sets of three structurally related compounds were investigated.

The first set concerns a group of azole derivates: itra-, keto- and miconazole. A second group of compounds are T1001 (loperamide), T263 and R731. The molecular formulas of the drugs are given in Fig. 1. All samples were obtained from Janssen Pharmaceutica (Beerse, Belgium). The purity of all products was

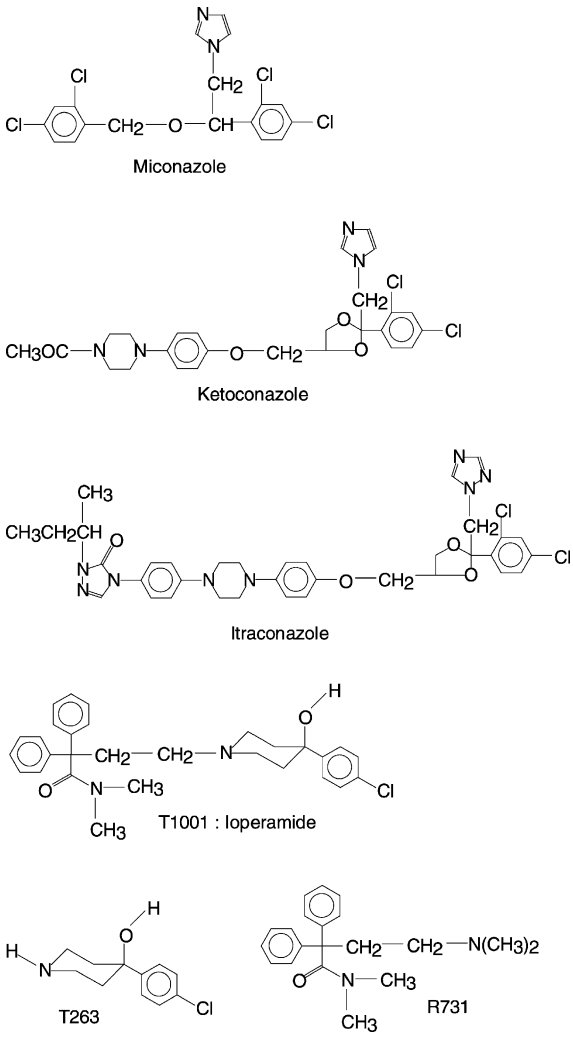

Fig. 1. Molecular structures of the drugs.

determined using appropriate HPLC-methods and was always more than 99.0%. TGA-measurements revealed that loperamide was actually a monohydrate.

All drugs were made amorphous in the DSC by cooling them from the melt at an appropriate rate to a temperature well below T_g.

2.2. Thermal analysis

Standard DSC-measurements, were performed on a Mettler-Toledo DSC822^e equipped with an intercooler and the results were analysed with the STAR^e software (Mettler-Toledo, Switserland). Mercury, water, octadecane, indium and tin were used to calibrate the temperature scale; enthalpic response was calibrated with indium and mercury. This apparatus also offers the possiblity to calibrate for tau lag, i.e. the influence of scan rate on the measured temperature. The calibration of temperature, enthalpy and tau lag was validated daily using the same standard materials: at least one randomly chosen sample was heated at a randomly chosen heating rate. Deviation of the experimental value from the theoretical one was less than 0.3 K for temperature measurement and less than 2.0% for enthalpy measurement.

Measurements performed at high cooling rates ($\geq$40 °C/min), were performed on a Perkin Elmer DSC 7 (Perkin-Elmer, CT, USA) equipped with a liquid nitrogen subambient accessory and the curves were analysed using the Pyris software version 3.6. For this apparatus it was sufficient to use two calibration standards for temperature calibration (indium and octadecane) and one for the enthalpic response (indium). Daily validation using the same standard materials showed that deviation of the experimental value from the theoretical one was less than 0.5 K for temperature measurement and less than 1.0% for enthalpy measurement.

Samples (weight range 2.00–3.50 mg) were analysed in hermetically sealed aluminium sample pans (TA Instruments, Mettler-Toledo), except for T1001 for which open pans (TA Instruments) or pans with a pierced lid (Mettler-Toledo) were used to allow for removal of water from the melt.

In order to study the influence of the rate of cooling from the melt on the position of the T_g, the crystalline drugs were heated to 10 K above their melting point and cooled at rates varying from 0.2 to 80 K/min to 30 K below T_g. Subsequently, the glassy materials were heated at 10 K/min to 10 K above their melting point. This last heating run was used to determine the glass transition temperature.

In order to study the influence of the heating rate on the glass transition temperature, drugs were heated to 10 K above their melting point and cooled at 20 K/min to 30 K below T_g. The glass transition temperature was determined in the subsequent heating run in which the heating rate was varied from 0.2 to 20 K/min.

3. Results and discussion

3.1. Influence of the cooling rate on the glass transition of T1001, T263 and R731

It was shown that all products could be obtained in the amorphous state by cooling them at the appropriate rate from the melt. The minimal cooling rates ($q_{-\min}$) are listed in Table 1. The results suggest that there is a relationship between the complexity of the molecules and the ease with which they can be vitrified. T1001 cannot be crystallized from the melt and during the subsequent reheating, the thermogram gives no indication for cold crystallization once the sample is being brought above its T_g. R731 and T263 can both be crystallized from the melt when the cooling rate is slow enough and even when the cooling is fast enough for vitrification to take place, a cold crystallization above T_g takes place in these samples during the subsequent reheating.

The experiments led to an intriguing phenomenon concerning the determination of the glass transition temperature during the second heating run. Fig. 2a and b shows the dependence of T_g on the cooling rate ($\ln q_-$) for R731 and T1001. Since T263 crystallizes quite easily upon cooling, only the fastest cooling rates ($\geq$10 K/min) led to an amorphous sample. Hence, for

Table 1
Minimal cooling rates required to obtain the amorphous drugs from the melt, together with the T_g-values measured after cooling at 10 K/min

Substance	$T_{g\,1/2c_p}$ (K)	T_{gr} (K)	$q_{-\min}$ (K/min)
T1001	339.0	336.9	0.2
R731	259.4	257.0	0.5
T263	294.2	292.2	10

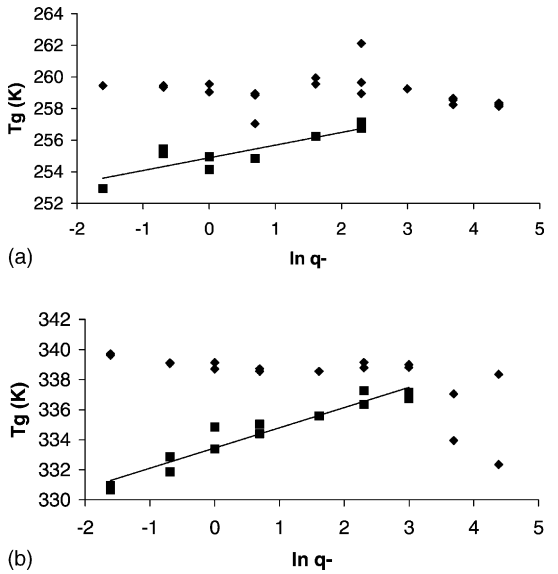

Fig. 2. Dependence of T_g on the cooling rate ($\ln q_-$) for R731 (a) and T1001 (b) (◆) $T_{g\,1/2c_p}$, (■) T_{gr}, (—) linear fit through (■).

this sample the number of experimental points to put in such a graph was limited and is not presented in this paper.

From these graphs it is evident that when the most common method for determination of T_g is used ($T_{g\,1/2c_p}$), there is a very small decrease of T_g with increasing cooling rate. If however the method developed by Richardson (1994) is being used (T_{gr}), T_g shows a clear decrease with decreasing cooling rate.

Upon cooling a substance from the melt, crystallization should take place from a thermodynamic point of view since the crystalline state is the energetically most stable one below the melting temperature. A discontinuous change in enthalpy, entropy and volume takes place at the melting point T_m, as is being visualized in Fig. 3a. However, if cooling is relatively fast, crystallization can be suppressed and the *H*-, *S*-, or *V*-curve corresponding to the liquid state is being followed. The material is now in the super-cooled liquid state, which is from a thermodynamic point of view not the most stable one. At a certain temperature the viscosity becomes extremely high so that molecular mobility is impaired and the material can no longer relax to the equilibrium conformation, characteristic for the super-cooled liquid at that particular temperature. Instead, it becomes a glass with a frozen-in molecular conformation typical of some higher temperature liquid. In this glass the viscosity is so high that it behaves like a solid and relaxation processes are very slow. The lowering of *H*, *S* and *V* upon cooling will be reduced in comparison to the equilibrium state.

When cooling is fast, the time required for relaxation and reduction of free volume in order to follow the curve of the liquid, is getting too long in comparison with the cooling rate at temperature T_A (Fig. 3a). When the cooling rate is lower, at each temperature the molecules get more time to reduce the free volume and the curve representing the liquid will be followed down to lower temperatures (T_B). Hence, temperature and time have an influence on the properties of a glass (aging). This is especially the case when the glass is only a few or a few tens of degrees below its T_g, where molecular mobility is reduced compared to the liquid

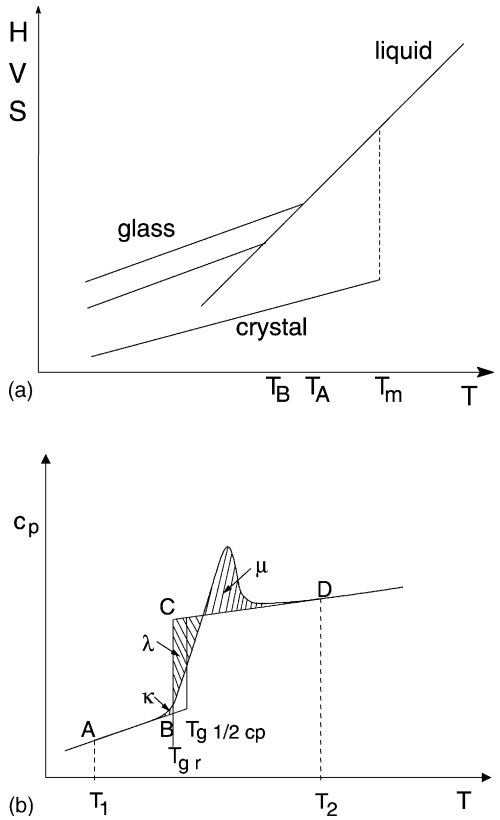

Fig. 3. (a) Change of enthalpy (*H*), entropy (*S*) and volume (*V*) as a function of temperature for a vitrifying and crystallizing material. (b) Schematic representation of two methods used to determine T_g.

state but still far from zero. Far below T_g aging becomes unimportant and the glass is said to be 'stable'.

This dependence from T_g on cooling rate is known from dilatometry, which measures volume changes with temperature. This technique was already in use long before DSC was available and defines T_g as the point of intersection of the *V*-curves corresponding to the glassy and the liquid state (Kovacs, 1963).

In DSC-measurements heat flow is registered, which is proportional to the heat capacity: $c_p = (dH/dT)_{P,V}$. Since the slope of the enthalpy curve changes at T_g (see Fig. 3a), a jump or shift in c_p (and hence in heat flow) takes place at this temperature. It must be emphasized that Fig. 3 is only a schematic representation and that the enthalpy curves in the glass transition region deviate from linearity. The extent of this deviation is related to aging phenomena and is strongly influenced by experimental conditions (time given to the sample at temperatures below but close to T_g). Hence, determination of T_g as the point of intersection should be performed on data from the 'stable' glass and liquid phase so that extrapolations from outside the glass transition region are required.

This deflection of linearity is also visible in the DSC-curves. Instead of a clear step-wise change in c_p an endothermic peak on top of this transition is registered in well-annealed samples. If the enthalpy curves would not be distorted by aging phenomena but would be linear also in the glass transition region, the shift in c_p as a function of temperature would appear as a clear vertical shift.

This brings us back to the anomalous results that were obtained when the influence of the cooling rate on T_g was presented. When the frequently used method for determining T_g was applied ($T_{g\,1/2c_p}$), the expected decrease of T_g with decreasing cooling rate was not observed (see Figs. 2a and b). In Fig. 3b the way to determine this T_g-value is depicted. An alternative method, originally described by Richardson (1994) and already applied in polymer science, is also illustrated in this graph. This method is based on enthalpic considerations. Integration of the c_p-function from point A to D (T_1 to T_2, both well away from the glass transition region) gives the enthalpy change of the substance between these two temperatures. Since enthalpy is a state function, this change in enthalpy between the 'stable' glass (at point A) and the liquid (at point D) is independent from the followed pathway. This method consists in drawing a vertical line as if the enthalpy curves would not deviate from linearity in the glass transition region. The temperature at which this line is drawn, is chosen in order to obtain equal surfaces (enthalpies) underneath the new c_p-curve (ABCD) and the original one. This requirement is met when $\lambda = \kappa + \mu$ (Flynn, 1974; Moynihan et al., 1976). Fig. 3b clearly illustrates that when enthalpy relaxation is important, $T_{g\,1/2c_p}$ leads to an overestimation of the T_g. For heating thermograms in which this endothermic signal is very small (after fast cooling) the deviation between $T_{g\,1/2c_p}$ and T_{gr} becomes smaller and in the extreme case where no annealing took place at all, they will coincide. The difference between the two T_g-values is illustrated in Table 1. Here, the values registered after cooling the different substances at 10 K/min are represented.

The dependence of T_{gr} on cooling rate agrees with basic theory and experience from dilatometric measurements. The value of this method is obvious from the results and the discussion above. Nevertheless, it has only been put into practice rather scarcely in polymer science and is fairly unknown in the field of pharmacy even though the use of other T_g-values (e.g. $T_{g\,1/2c_p}$) can lead to anomalous conclusions.

3.2. Evaluation of two methods used to study molecular mobility below T_g of itraconazole, ketoconazole and miconazole

The second part of this report, focuses on looking for a qualitative correlation between two existing methods to evaluate molecular mobility below T_g.

The first one concerns the calculation of the mean molecular relaxation time based upon DSC measurements. This method had already been applied in our laboratory on three azole derivates, hence, these molecules were chosen for this comparative study.

Table 2 summarizes the τ- and β-values obtained for miconazole, ketoconazole and itraconazole at different temperatures below T_g, with τ being the mean relaxation time constant and β a parameter describing the distribution of the molecular relaxation times (Hancock et al., 1995; Van den Mooter et al., 1999; Di Martino et al., 2000). A value of 1 indicates a single relaxation time for all molecules.

It is clear that close to T_g, τ is still very small for all products, indicating a low stability. As the annealing

Table 2
τ- and β-values for the different azole derivates (Van den Mooter et al., 2001; Six et al., 2001)

$T_g - T$ (K)	β	τ (h)
Itraconazole		
10	0.43 (±0.01)	23.47 (±1.30)
25	0.48 (±0.01)	17.27×10^2 ($\pm 10.03 \times 10^1$)
30	0.59 (±0.01)	58.76×10^2 (±768.98)
40	0.44 (±0.01)	7.01×10^5 ($\pm 1.29 \times 10^5$)
Ketoconazole		
12	0.42 (±0.05)	15.88 (±3.03)
22	0.55 (±0.08)	82.31 (±17.56)
32	0.53 (±0.09)	1.04×10^3 ($\pm 1.72 \times 10^2$)
42	0.39 (±0.02)	4.21×10^5 ($\pm 7.46 \times 10^4$)
Miconazole		
12	0.27 (±0.01)	38.14 (±0.20)
27	0.60 (±0.03)	170.50 (±31.50)
42	0.33 (±0.01)	1.13×10^5 ($\pm 1.41 \times 10^4$)

temperature decreases, τ becomes larger. Especially at the lowest temperatures, the difference in τ between the molecules becomes clear, with itraconazole being the most stable one (largest τ), followed by ketoconazole and then miconazole. This order is in agreement with the molecular size and complexity of these analogues (see Fig. 1).

In the second method, we investigated the influence of the heating rate on the measured T_g. Since for these experiments a constant cooling rate was being used, during cooling the same (let us say the upper) *H*-, *S*- or *V*-curve corresponding to the glassy state was being followed (see Fig. 3a) and identical glasses were being formed. Hence, one would expect a constant T_g in the subsequent heating (independent from the applied heating rate). However, relaxation can take place during the subsequent heating since molecular mobility is not zero in the glassy state and becomes more important as T_g is being approached. When heating is fast, the time given to the sample to decrease its free volume and to evolve to a more compact glass (with lower *V*, *H* and *S*), is short. When on the other hand heating is slow, the glass has a longer period of time to anneal. This annealing comes down to a movement from the upper curve corresponding to the glassy state in Fig. 3a, to the lower curve. The intersection of this lower curve with the curve representing the liquid is situated at lower temperature ($T_B < T_A$).

Whether or not a dependence of T_g on heating rate will be observed depends on the determination procedure. If the lower limit for the determination of T_g is set far below the glass transition (at least 50–60 K below T_g), the measured T_g will not depend on heating rate since at this lower limit, relaxation phenomena are negligible and for all measurements the glass transition of the originally formed glass will be registered. If however the lower limit is set relatively close to the

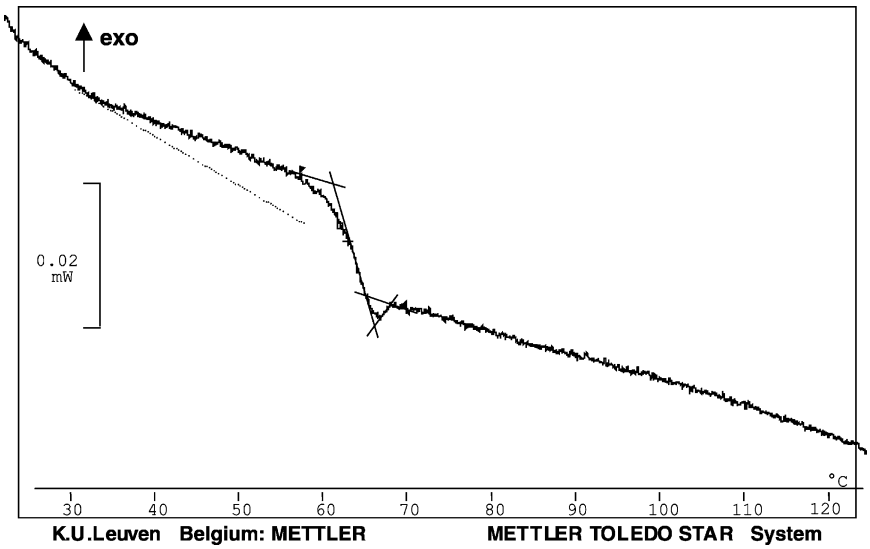

Fig. 4. Example of a sample heated at low heating rate (0.5 K/min), indicating annealing below T_g during the heating run.

glass transition region, an influence of the heating rate arises. When low heating rates are being applied, enhanced annealing conditions are being reached and relaxation during heating becomes more important. This relaxation can clearly be detected in the DSC-curves. In Fig. 4, an example is given of a sample that is being heated at 0.5 K/min. A deviation from the baseline due to relaxation takes place below T_g. Hence, if the T_g is being determined by drawing a tangent to this deviating part of the heat flow curve, the obtained T_g corresponds to the annealed sample and not the glass that was originally formed upon cooling. Plots of $\ln q_+$ versus $1/T_g$ were constructed and are represented in Fig. 5a–c. From these plots the activation energy for the transition from the glassy to the super-cooled liquid state can be obtained.

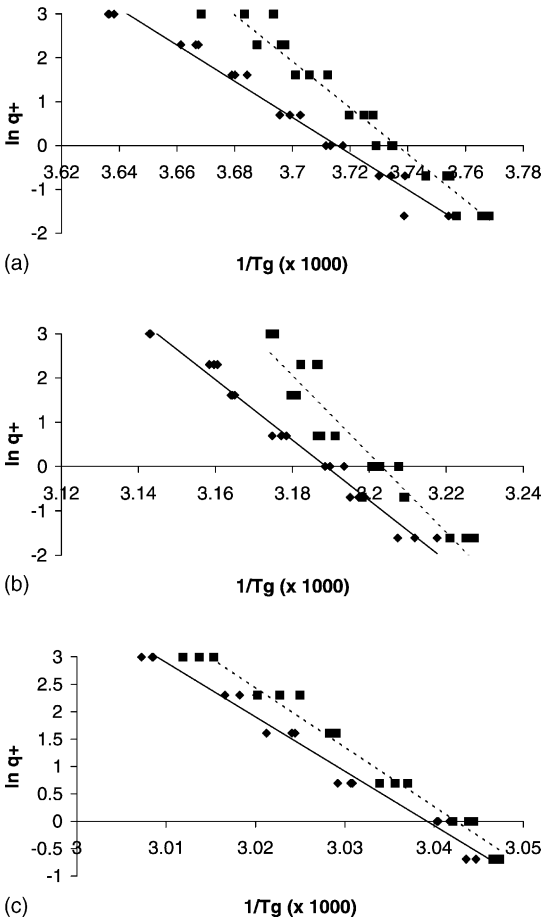

Fig. 5. Plots of $\ln q_+$ vs. $1/T_g$ (K^{-1}) for miconazole (a), ketoconazole (b) and itraconazole (c) (◆) $T_{g\,1/2c_p}$, (■) T_{gr}, (- - -) linear fit through (■), (—) linear fit through (◆).

The graphs clearly show that the curves based upon the T_{gr}-values have a higher negative slope than the ones based upon the $T_{g\,1/2c_p}$-values, leading to a higher activation energy. This is especially the case for the two smallest molecules.

The deviation between T_{gr} and $T_{g\,1/2c_p}$-values is known to increase when the endothermic signal on top of the glass transition increases (see Fig. 3b). Since annealing conditions are being improved as the heating rate becomes smaller, one would expect the largest deviation at low q_+ (and low $\ln q_+$). This is however the opposite of what the graphs show. This can be explained by the fact that the T_gs were determined from heat flow curves and not c_p-curves. These heat flow curves are proportional to the c_p-curves, multiplied by the heating rate. Hence, in measurements performed at high heating rates, these heat flow curves show a large shift in the glass transition region, accompanied by a large endothermic effect since all calorimetric effects are being enlarged. The recuperation of enthalpy is not bigger than when low heating rates are being applied; as a matter of fact it is even smaller, but it has to take place over a shorter period of time.

For itraconazole, the difference between the two plots is notably smaller than for the other two substances. This is caused by the fact that enthalpy recuperation is far less important, which is clear from a comparison of the DSC-thermograms and which is an additional indication for a higher stability of itraconazole in the glassy state: it seems to be less susceptible to relaxation phenomena.

Table 3 summarizes the activation energies for the three substances, based on the two different methods for determining T_g. The following conclusions can be drawn.

E_a based on $T_{g\,1/2c_p}$ is always smaller than E_a based on the T_{gr}-values. The origin of this phenomenon is

Table 3
Activation energies for the different azole derivates

Substance	E_a ($T_{g\,1/2c_p}$) (kJ/mol)	E_a (T_{gr}) (kJ/mol)
Itraconazole	824.9	904.7
Ketoconazole	566.6	731.4
Miconazole	342.9	442.0

explained above. Itraconazole has the highest activation energy and miconazole the lowest. This means that the barrier that has to be overcome in order to devitrify the sample is the highest for itraconazole, which can be interpreted as an indication of stability.

A comparison of the two methods also leads to some interesting conclusions.

The methods are in agreement with each other as they both indicate that itraconazole forms the most stable glass, followed by ketoconazole and then miconazole. They can both be used to draw conclusions concerning molecular mobility below T_g. The first one gives an idea about the absolute value for the time scale during which a glassy substance can be safely stored but has the disadvantage that it is very time consuming. The second method only allows to make a comparison between structurally related compounds as far as stability is concerned. The time required to carry out the experiments is however much shorter.

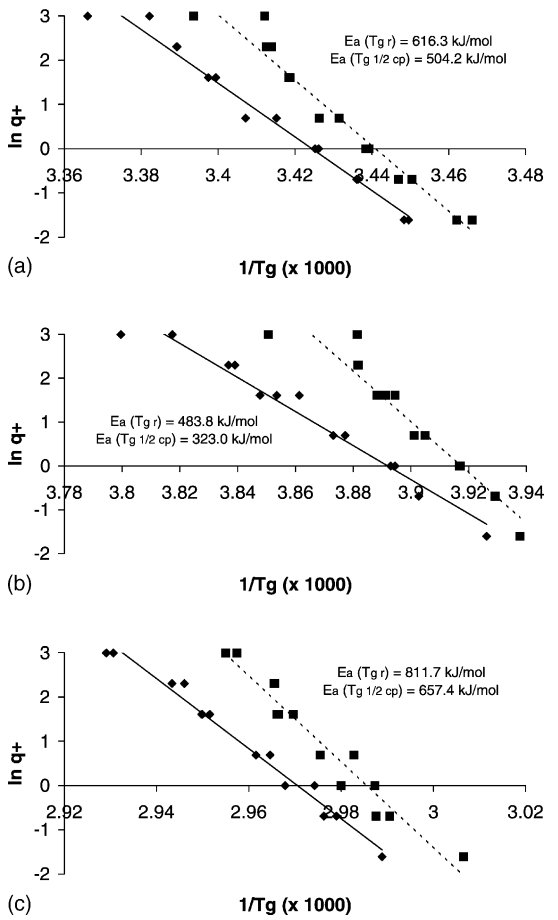

Fig. 6. Plots of $\ln q_+$ vs. $1/T_g$ (K^{-1}) for T263 (a), R731 (b) and T1001 (c) (◆) $T_{g\,1/2c_p}$, (■) T_{gr}, (- - -) linear fit through (■), (—) linear fit through (◆).

3.3. Evaluation of the molecular mobility below T_g for loperamide and its two derivates

Due to the fact that the second method is less complex and much faster, the molecular mobility of these molecules was evaluated by examination of the dependence of T_g on heating rate q_+. Fig. 6a–c shows the plots of $\ln q_+$ versus $1/T_g$. From these graphs the activation energies could be calculated, which are given in the same figure.

For these products as well, the difference between the plots of $\ln q_+$ versus $T_{g\,1/2c_p}$ and $\ln q_+$ versus T_{gr} is clear and they lead to different values for the activation energy. Since the determination of T_{gr} is more accurate, preference is given to the activation energies obtained based upon these plots.

It is clear that also for these three products the most complex one, forms the most stable glass; loperamide has the highest activation energy.

4. Conclusion

The results of the present study showed that the values of the activation energy for the transition of a glass to its super-cooled liquid state qualitatively correlate with the values of the mean molecular relaxation time constant of ketoconazole, itraconazole and miconazole, three structurally related drugs. Estimation of the molecular mobility by activation energy calculation indicated that loperamide was more stable than its two building blocks T263 and R731. We further showed that the commonly used approach to determine T_g ($T_{g\,1/2c_p}$) leads to erroneous values when enthalpy recovery is significant. In this case, an alternative method based on enthalpic considerations leads to results in accordance to basic thermodynamics. Estimation of molecular mobility based on activation energy calculations is therefore considered to be a valuable alternative for the method based on measurement of the extent of relaxation. When enthalpy relaxation is important, the use of $T_{g\,1/2c_p}$ leads to an overestimation of the T_g.

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