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Characterization of glassy itraconazole: a comparative study of its molecular mobility below T_g with that of structural analogues using MTDSC

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Abstract

The objective of the present study was to estimate the molecular mobility of glassy itraconazole below the glass transition, in comparison with structural analogues (i.e. miconazole and ketoconazole).

Glassy itraconazole and miconazole were prepared by cooling from the melt. The glassy state of the drug was investigated with modulated temperature DSC using the following conditions: amplitude ± 0.212 K, period 40 s, underlying heating rate 2 K/min. The glass transition was determined from the reversing heat flow and occurred at 332.4 (± 0.5) K and 274.8 (± 0.4) K for itraconazole and miconazole, respectively. The jump in heat capacity at the glass transition was 303.42 (± 3.43) J/mol K for itraconazole and 179.35 (± 0.89) J/mol K for miconazole. The influence of the experimental conditions on the position of the glass transition of itraconazole was investigated by varying the amplitude from ± 0.133 to ± 0.292 K and the period from 25 to 55 s, while the underlying heating rate was kept constant at 2 K/min. Glass transition temperature, T_g, was not significantly influenced by the frequency of the modulation nor by the cooling rate. However, the relaxation enthalpy at the glass transition increased with decreasing cooling rate indicating relaxation during the glass formation process. To estimate the molecular mobility of the glassy materials, annealing experiments were performed from $T_g - 10$ to $T_g - 40$ K for periods ranging from 15 min to 16 h.

Fitting the extent of relaxation of glassy itraconazole to the Williams–Watts decay function and comparing the obtained values with those of amorphous miconazole and ketoconazole indicated that the molecular mobility is influenced by the complexity of the molecular structure. The more complex the structure, the more stable the amorphous state.

Keywords: Itraconazole; Modulated temperature DSC; Molecular mobility; Amorphous drugs

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1. Introduction

The formulation of solid dispersions has already been proposed in 1961 to overcome dissolution rate limited oral absorption (Sekiguchi and Obi, 1961). Despite the fact that more than 500 papers on solid dispersions have been published in the pharmaceutical literature since then, few drug products relying on this technique have reached the market, mainly because of physical–chemical stability and upscaling problems. Indeed, the formulation of solid dispersions often transforms the physical state of the drug, leading to amorphous or partially amorphous drugs. Although the amorphous state is a high-energy state resulting in enhanced dissolution rate, from a thermodynamical point of view, it is a metastable state and recrystallization from the amorphous state is theoretically inevitable. However, if the time scale of devitrification is very large, it can be considered irrelevant with respect to drug stability. In this respect, the glass transition temperature, T_g, is a key parameter, as it indicates the borderline between a temperature domain of low- and high-molecular mobility, whereas the relaxation endotherm that accompanies the glass transition indicates the magnitude of the molecular mobility below the glass transition. In the present paper, we report on the molecular relaxation times of glassy itraconazole, a member of the triazole antifungals, as a measure of its stability. To investigate the influence of the molecular structure of itraconazole on its glassy stability, the molecular relaxation times will also be determined for miconazole, which can be considered as ''a building block'' of itraconazole. In a previous study, we observed that amorphous ketoconazole, an imidazole antifungal agent, which can be situated between itraconazole and miconazole with respect to its structure, showed a negligible molecular mobility at 42 K below its T_g (Van den Mooter et al., 2000). It is the objective of this paper to investigate whether increasing complexity in molecular structure has an influence on the molecular mobility of the glassy compounds and, hence, on their stability. Standard or conventional DSC has been used in previous studies (Hancock et al., 1995; Van den Mooter et al., 1999) to calculate the molecular mobility in order to relate it to the stability of amorphous drugs. However, the presence of the relaxation endotherm over the glass transition region prevents accurate determination of both transitions. As the glass transition is a function of the cooling rate while the endothermic relaxation is a function of absolute temperature and time, modulated temperature DSC (MTDSC) offers the possibility to separate and quantitate both transitions accurately. Royall et al. (1998) and Hill et al. (1998) showed the applicability of this relatively new technique in the area of pharmaceutical sciences. MTDSC allows deconvolution of the total heat flow into a component that is related to the heat capacity and the heating rate (reversing signal) and one that is a function of any kinetically hindered event (non-reversing signal)(Reading et al., 1993; Reading, 1993).

2. Materials and methods

2.1. Materials

Itraconazole and miconazole (microfine grade) were a generous gift of Janssen Pharmaceutica (Beerse, Belgium). The water content of the drugs was less than 0.1% w/w (Karl Fisher titration), and were stored in a dessicator containing P2O5 until use. The glassy drugs were prepared from the crystalline state in the MTDSC by cooling the melted drug to 40 K below its glass transition temperature at a rate of 20 K/min.

2.2. Thermal analysis

MTDSC measurements were carried out using a 2920 modulated DSC (TA Instruments, Leatherhead, UK), equipped with a refrigerated cooling system (RCS). Data were treated mathematically using the Thermal Solutions software (TA Instruments, Leatherhead, UK). Dry helium at a flow rate of 40 ml/min was used as the purge gas through the DSC cell and 150 ml/min of nitrogen through the RCS unit. TA Instruments (Leatherhead, UK) aluminium hermetic pans were used throughout the study; the mass of each empty sample pan was matched with the mass of

the empty reference pan to ± 0.1 mg. The weight of the sample was always between 2.00 and 4.30 mg.

Octadecane, benzoic acid, cyclohexane and indium standards were used to calibrate the DSC temperature scale; enthalpic response was calibrated with indium. The heat capacity signal was calibrated by comparing the response of dry, powdered aluminum oxide to the equivalent literature value in the glass transition region of itraconazole and miconazole. Validation of temperature, enthalpy and heat capacity measurement 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, whereas it was less than 0.1% for enthalpy measurement and less than 0.75%, 1% and 1.25% for measurement of the heat capacity at 329.85, 299.85 and 279.85 K, respectively.

In order to determine the T_g of itraconazole and miconazole, the crystalline drug was heated to 10 K above the melting point, cooled to 292.4 and 234.8 K at 20 K/min, respectively, and reheated at an underlying heating rate of 2 K/min, a period of 40 s and an amplitude of ± 0.212 K. The samples were always equilibrated for 10 min before starting the temperature modulation.

The influence of the cooling rate on the position of the glass transition of itraconazole was determined by cooling the liquid drug from the melt to 292.4 K at a rate of 0.2, 2, 5, 10 and 20 K/min, followed by reheating the glass at an underlying heating rate of 2 K/min, a period of 40 s and an amplitude of ± 0.212 K to 40 K above T_g. The influence of the amplitude and the period on T_g was investigated by heating glassy itraconazole from 307.4 to 10 K above T_g at an underlying heating rate of 2 K/min, while the period and the amplitude were varied from 25 to 55 s, and from ± 0.113 to ± 0.292 K, respectively.

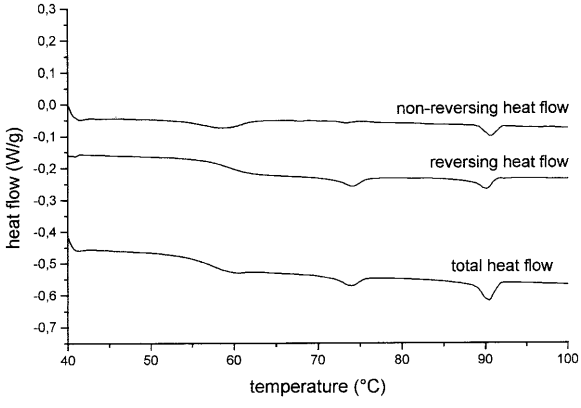

Fig. 1. The total, reversing and non-reversing heat flow of glassy itraconazole during a heating run.

Annealing experiments were performed by cooling liquid itraconazole or miconazole from the melt at 20 K/min to the ageing temperatures, which were $T_g - 10$, $T_g - 25$, $T_g - 30$, and $T_g - 40$ K. The glass was annealed at the different temperatures for either 15 min, 1, 2, 4, 8, or 16 h, before it was reheated to 10 K above T_g, at an underlying heating rate of 2 K/min, a period of 40 s and an amplitude of ± 0.212 K.

2.3. Data analysis

The optimal set of the mean relaxation time constant, τ, and the relaxation time distribution parameter, β, values for fitting of the experimental data was calculated using the Levenberg–Marquardt minimization procedure provided in the Origin software version 5.0 (Microcal Software Inc., USA).

3. Results and discussion

Crystalline itraconazole and miconazole can be transformed to the glassy state by cooling it from the melt. A representative thermogram of glassy itraconazole is shown in Fig. 1. As shown in this figure, reheating glassy itraconazole shows two endothermic peaks situated at 347 and 363 K. Elucidation of the nature of these peaks is the subject of current research. Preliminary data indicate mesophase formation. Calculation of T_g for itraconazole and miconazole from the total heat flow curve gives a value of 330.9 (± 0.4) and 271.9 (± 0.6) K, respectively. By multiplying the heat capacity with the underlying heating rate, the reversing signal can be obtained, and subtraction of the reversing from the total heat flow yields the non-reversing heat flow. As shown in Fig. 1, the

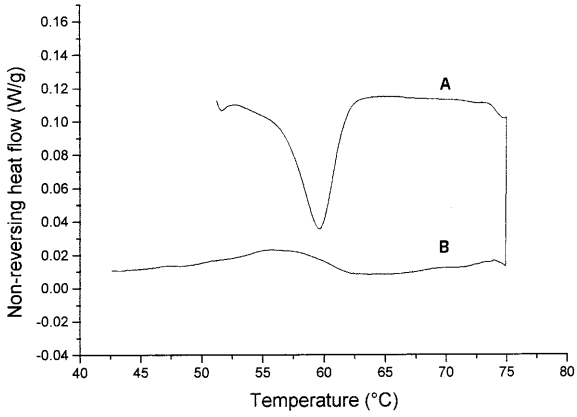

Fig. 2. MTHDSC response of glassy itraconazole in the non-reversing heat flow: A = heating run and B = cooling run.

glass transition appears in the reversing signal, whereas the relaxation endotherm appears in the non-reversing signal. Calculation of T_g from the reversing heat flow by taking the derivative with respect to temperature yields a value of 332.4 (± 0.5) and 274.8 (± 0.4) K for itraconazole and miconazole, respectively. These values are slightly higher than those calculated from the total heat flow curve, mainly because the reversing signal represents the response to the modulation, rather than the underlying heating rate, which is slower. In addition, the presence of the relaxation endotherm over the glass transition region hinders the determination of T_g from the total heat flow and leads to an underestimation. The onset of the relaxation endotherm for itraconazole was situated at 326.4 K; its magnitude was 1147.37 J/mol. As the reversing heat flow is dependent on the experimental conditions (frequency effect), the non-reversing heat flow (obtained by subtraction of the reversing from the total heat flow) will be overestimated and should be corrected. Cooling the sample after the heating run using the same experimental conditions enable to calculate this overestimation. A more detailed discussion of this frequency effect is given elsewhere (Royall et al., 1998; TA Instruments Modulated DSC Compendium, 1997). A typical cooling run is shown in Fig. 2. The peak observed in the non-reversing heat flow signal has no physical meaning; it is solely due to this frequency effect. The enthalpy was calculated to be 793.84 J/mol. Subtracting this value results in the correct value for the enthalpy of relaxation: 353.53 J/mol.

To investigate the influence of the applied period and amplitude on T_g of itraconazole, the period was varied from 25 to 55 s, while the amplitude was changed from ± 0.113 to ± 0.292 K, the underlying heating rate was kept constant at 2 K/min. Fig. 3a and Fig. 3b show the lissajous figures of itraconazole in the glass transition region using modulation parameters with period of 40 s and amplitude of ± 0.212 K and a period of 55 s and amplitude of ± 0.133 K, respectively. Lissajous figures can be used to investigate the harmonic response of a system to an applied harmonic stimulus (Hill et al., 1998). Modulation parameters with period of 40 s and amplitude of ± 0.212 K produces an elliptic lissajous figure indicating that the system is able to follow the modulation and working under steady state. On the other hand, using a period of 40 s and an underlying heating rate of 2 K/min, implicates that ± 0.212 K is the highest amplitude which can be used without cooling the sample periodically during a run.

Fig. 4 shows T_g as a function of the different periods used. Only a minor increase with increasing frequency can be observed (consecutive data points were statistically not significantly different). In theory, it is possible to use the frequency dependency of T_g to get information about the kinetics of the glass transition (Lacey et al., 1997). However, the frequency dependency was very small in this case and no conclusive statements can be made, strongly suggesting that MTDSC is not suited for studying frequency effects of small organics, because their glass transition region, as opposed to that of polymers, is rather narrow; in the case of itraconazole, it is approximately 10 K wide. This definitely limits the use of high periods, as it is necessary to have at least five modulation cycles over the transition region. The contribution of kinetically hindered thermal events to the total heat flow can give rise to a cosine contribution, assuming that most kinetically hindered responses can be modelled to a good approximation by an Arrhenius model, this cosine contribution can be made insignificantly small by ensuring that there

are many cycles over the transition (Jones et al., 1997). As the applied algorithm is based on this assumption, the frequency of the modulation and the underlying heating rate must be adjusted properly to ensure that this criterion is met, and not doing so would invalidate the use of the

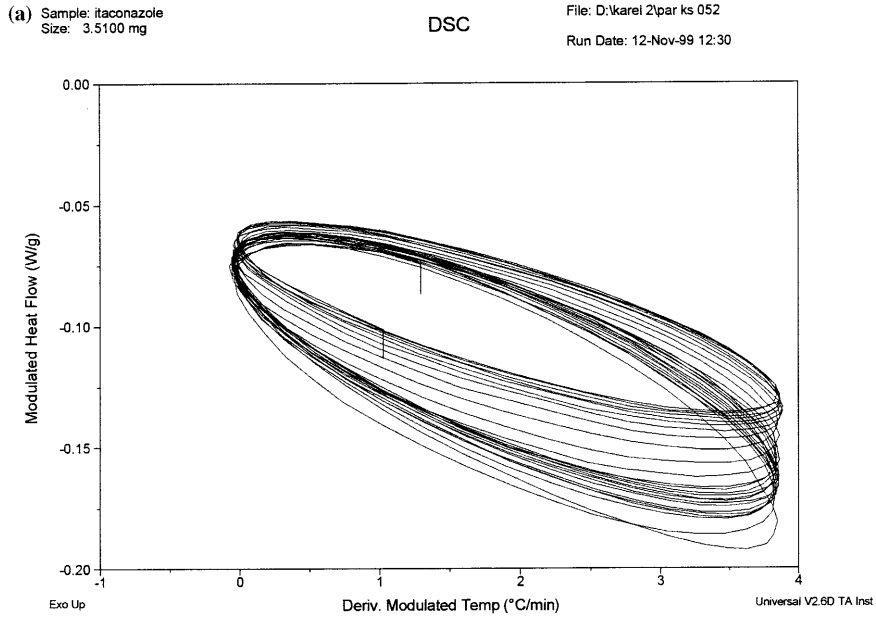

Fig. 3a. Lissajous figure in the glass transition region of itraconazole: period = 40 s and amplitude = ±0.212 K.

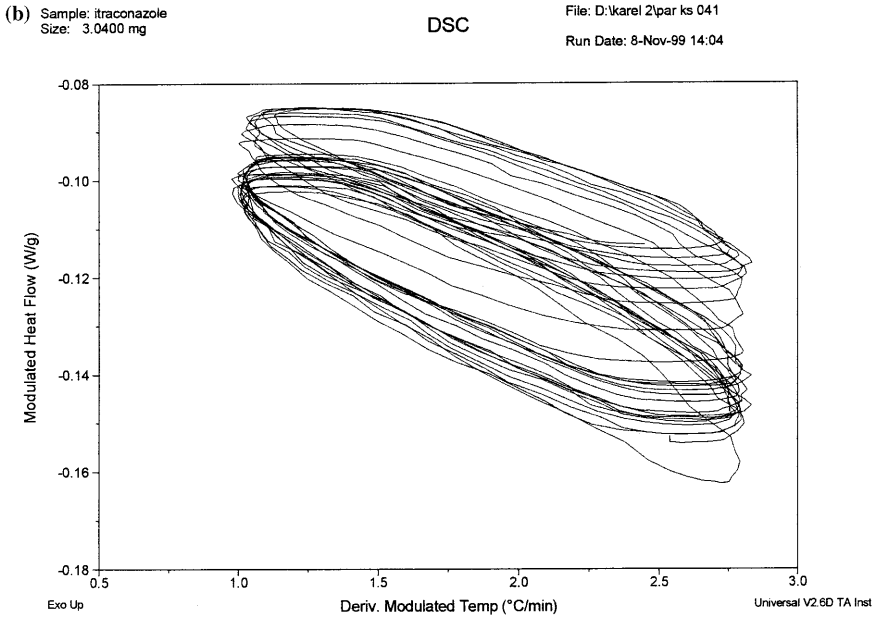

Fig. 3b. Lissajous figure in the glass transition region of itraconazole: period = 55 s and amplitude = ±0.133 K.

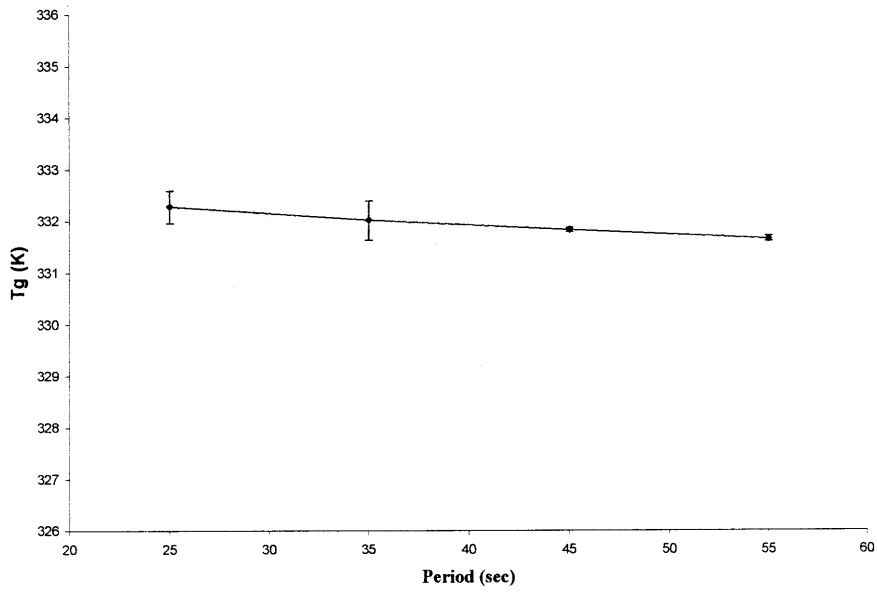

Fig. 4. Influence of the modulation period on the T_g of itraconazole.

technique. On the other hand, high frequencies should not be used anyway, because the DSC cell is not able to maintain the imposed modulation in that case.

Glassy itraconazole was further characterized by investigation of the influence of the cooling rate on the position of T_g and the magnitude of the accompanying relaxation endotherm. The results are summarized in Table 1. Changing the cooling rate did not influence T_g, although one could expect a decrease of T_g when decreasing the cooling rate (Moynihan et al., 1996). Indeed, at high temperatures, the molecules exhibit liquid-like behaviour for a characteristic time interval, and decreasing the temperature increases the relaxation times relative to this interval. At low temperatures, the relaxation times will be very large, and no relaxation is occurring; the material will exhibit glass-like behaviour. Decreasing the cooling rate will increase the characteristic time scale, and since relaxation times decrease with increasing temperature, the glass transition region should be shifted to lower regions. The fact that this is not observed in our experiments is an indication of short relaxation times of glassy itraconazole relatively to this characteristic time interval for the cooling rates applied. Decreasing the cooling rate from 20 to 0.2 K/min led to an increase of the relaxation enthalpy from 16.65 ($\pm$2.7) to 1383.05 ($\pm$12.1) J/mol. The decrease of the relaxation enthalpy with increasing cooling rate indicates that relaxation to the equilibrium state already starts during the formation of the glass. Since calculation of the molecular mobility below the glass transition is based on quantification of this relaxation endotherm, the above-mentioned observation should be taken into account; otherwise, one would overestimate the molecular mobility leading to invalid conclusions concerning the stability of amorphous materials. Fig. 5 shows the enthalpy recovery of itraconazole as a func-

Table 1
Influence of cooling rate on relaxation enthalpy and T_g[a]

Cooling rate (K/min)	ΔH (J/mol)	T_g (K)
0.2	1383.05 (12.1)	332.3 (0.2)
1	719.75 (16.4)	332.3 (0.1)
2	461.49 (20.5)	332.5 (0.1)
5	287.9 (9.8)	332.9 (0.2)
20	16.65 (2.7)	332.8 (0.3)

[a] The standard deviation is indicated in parenthesis.

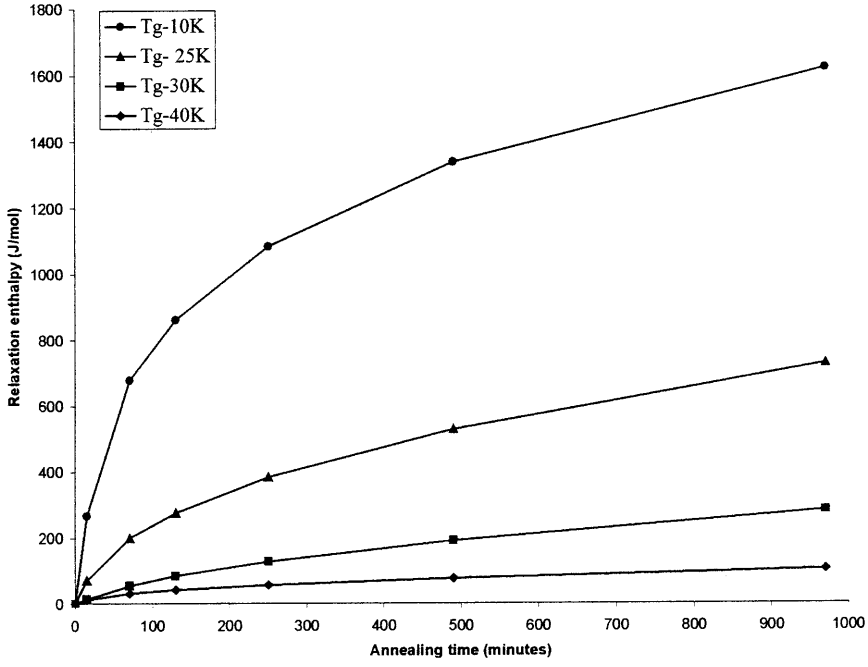

Fig. 5. Relaxation enthalpy of glassy itraconazole after annealing at different conditions.

tion of the annealing time after correction for the relaxation during the cooling step and this enthalpy recovery reflects the relaxation to the equilibrium state at the different ageing temperatures. The relaxation enthalpy of the drug increases with increasing ageing time, but decreased with decreasing ageing temperature in a non-linear way. It can be assumed that there is a maximal value of the relaxation enthalpy for every ageing temperature: $\Delta H_\infty = \lim_{(t\to\infty)} \Delta H$. At ageing temperatures far below T_g, relaxation times will become very large, therefore, ΔH_∞ can only be determined accurately at ageing temperatures near the T_g (Montserrat, 1994). However, in order to determine approximate values of ΔH_∞, one can either extrapolate the liquid enthalpy curve down to temperatures below the glass transition region, or when it is assumed that the heat capacity change (ΔC_p) is independent of the temperature, ΔH_∞ for a particular ageing temperature T can be calculated using the following equation:

$$\Delta H_\infty = (T_g - T)\Delta C_p$$

The complex heat capacity change (ΔC_p) of itraconazole and miconazole at the glass transition was determined to be 303.42 ($\pm$3.43) J/mol K and 179.35 ($\pm$0.89) J/mol K, respectively. Although theoretically, a decrease in configurational molecular mobility should be reflected in a decrease in heat capacity (Shamblin et al., 1999), isothermal ageing did not lead to a detectable decrease in heat capacity in our experiments.

By introducing a relaxation function, Φ_t, describing the extent of relaxation, the time scale of relaxation can be determined:

$$\Phi_t = \frac{[H(T_x,t_x) - H_\infty(T_x)]}{[H(T_x,t_x) - H_\infty(T_x)]} \; or \; \Phi_t = 1 - \frac{\Delta H}{\Delta H_\infty}$$

$$\Phi_t = \frac{[H(T_x,t_x) - H_\infty(T_x)]}{[H(T_x,t_0) - H_\infty(T_x)]} \quad \text{or } \Phi_t = 1 - \frac{\Delta H}{\Delta H_\infty}.$$

By fitting the extent of relaxation to the Williams–Watts two parameter relaxation function (Williams and Watts, 1970), one obtains a value for the mean relaxation time constant τ.

$$\tau \; . \; \Phi_t = \exp - \left[\frac{t}{\tau}\right]^\beta$$

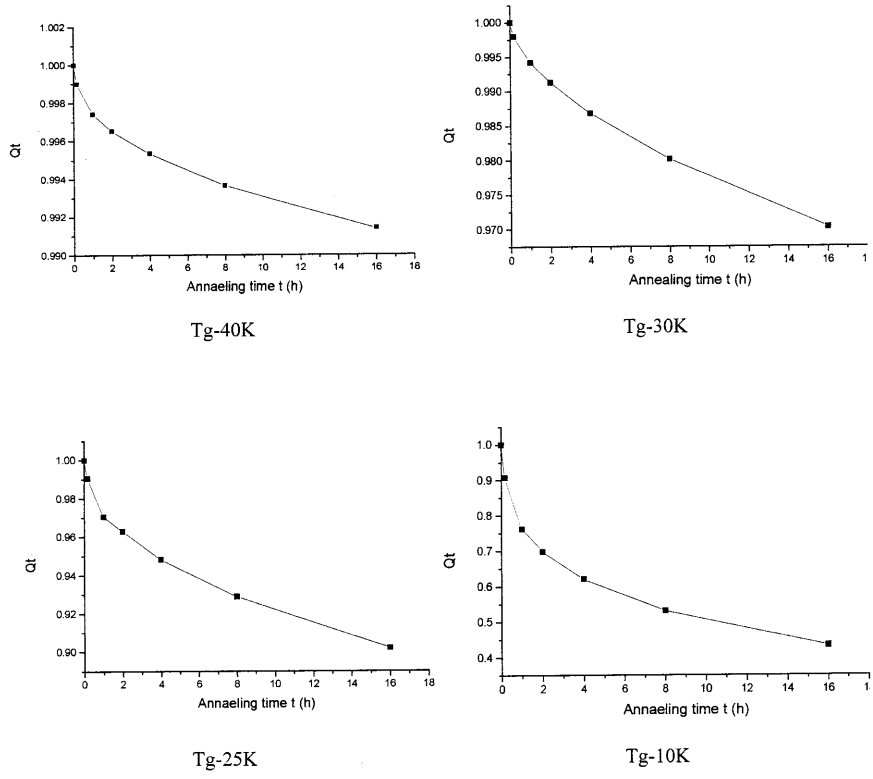

Fig. 6. Plot of the relaxation function of itraconazole at $T_g - 10$, $T_g - 25$, $T_g - 30$, and $T_g - 40$ K.

This empirical decay function was originally developed to describe non-symmetrical dielectric relaxation behaviour, and has since then frequently been applied to quantify the structural relaxation process in glassy polymers (Gomez Ribelles et al., 1987; Cowie and Ferguson, 1989; Ten Brinke and Grooten, 1989). In this equation, β is a parameter, which describes the distribution of the molecular relaxation times, and consequently ranges between 0 and 1, where the latter indicates a single relaxation time for all molecules. Fig. 6 (a, b, c, and d) shows the extent of relaxation for itraconazole calculated with the Williams–Watts decay function, as a function of the ageing time t. The calculated parameters are summarized in Table 2 and indicate that fitting of the data to the two parameter decay function was satisfactory. The value of β ranges from 0.4249 to 0.5928 for itraconazole and from 0.2688 to 0.5969 for miconazole, and were always statistically significantly different from 1, indicating a distribution of relaxation time scales, rather than a single relaxation time; this is consistent with heterogeneity in molecular motions. Although Craig et al. (2000) recently calculated relaxational behaviour of amorphous lactose using a fixed value for β

Table 2
Calculated parameters of the Williams–Watts decay function[a]

$T_g - T$ (K)	β	τ (h)
Miconazole		
12	0.27 (0.01)	38.14 (0.2)
27	0.60 (0.03)	170.50 (31.50)
42	0.33 (0.01)	1.13×10^5 (1.41×10^4)
Itraconazole		
10	0.43 (0.01)	23.47 (1.30)
25	0.48 (0.01)	17.27×10^2 (10.03×10^1)
30	0.59 (0.01)	58.76×10^2 (768.98)
40	0.44 (0.01)	7.01×10^5 (1.29×10^5)

[a] The standard deviation is indicated in parenthesis.

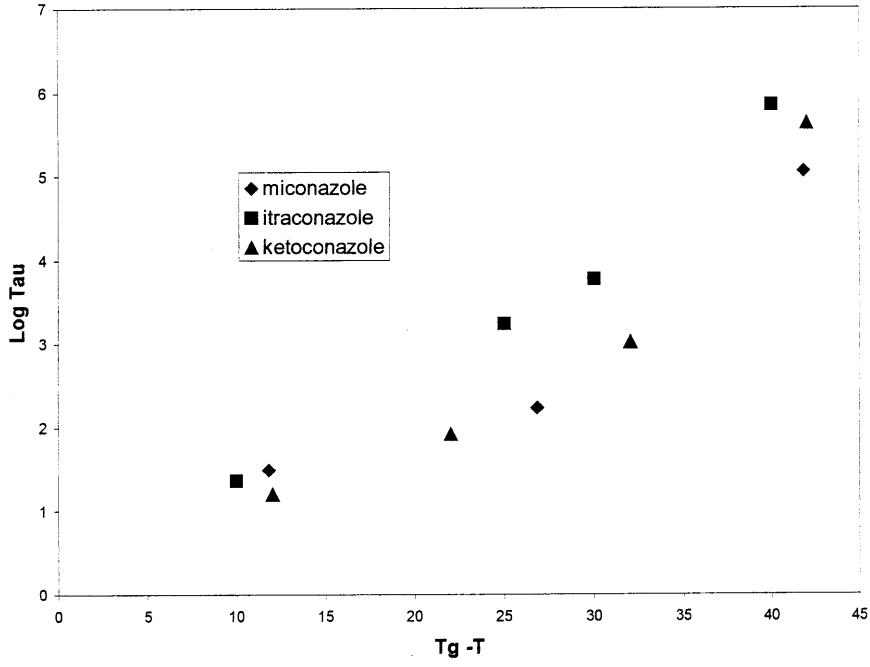

Fig. 7. Plot of log mean relaxation time constant versus the scaled temperature for glassy itraconazole.

(equal to 1), the current, as well as previously published data (Van den Mooter et al., 1999; Hancock et al., 1995; Di Martino et al., 2000), support the treatment of β as an adjustable parameter, rather than a fixed one.

When the three structural analogues are compared, it is clear that the mean relaxation time constant always increases at lower annealing temperatures. Fig. 7 shows a plot of log τ as a function of the scaled temperature $T_g - T$. The magnitude of the mean relaxation time constant differs for the three analogues, itraconazole having the highest τ values, miconazole the lowest and ketoconazole in between. This indicates that itraconazole is more stable than ketoconazole and ketoconazole is more stable than miconazole. This difference in stability can be explained, at least partially, by the increasing complexity of the structures (Fig. 8). Miconazole is the smallest molecule and for that reason it will be easier to relax while itraconazole is more complex, and it can be assumed that steric hindrance is more important in the latter case. These observations need to be further investigated using a series of structural analogues in order to establish a possible structure/response relationship.

While it was previously stated that amorphous drugs should be stored at least 50 K below there T_g (Hancock et al., 1995), the present investigation refines this statement. Indeed the data obtained in this report show that molecular mobility below T_g is related to the molecular structure and glassy molecules with a more complex structure can therefore be stored at slightly higher temperatures.

4. Conclusion

In the present report, glassy itraconazole was characterized using MTDSC. The crystalline drug was transformed to the glassy state by cooling from the liquid state; irrespective of the cooling rate, itraconazole formed a glass by a T_g of 332.4 ($\pm$0.5) K. The position of the glass transition was not influenced by a change in the modulation frequency, nor by changing the cooling rate, while the magnitude of the relaxation endotherm over

the glass transition increased with decreasing cooling rates, indicating that relaxation already starts during the formation of the glass. MTDSC allowed accurate determination of the relaxation enthalpy in the non-reversing heat flow. Fitting the extent of relaxation of glassy itraconazole to the Williams–Watts decay function and comparing the obtained values with structural analogues such as miconazole and ketoconazole, showed that the molecular mobility seems to depend on the molecular structure: the more complex the structure, the more stable the amorphous state.

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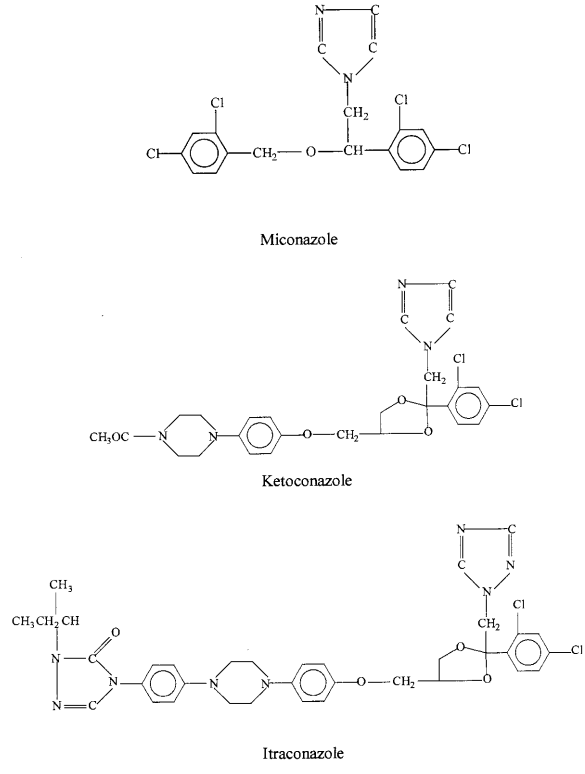

Fig. 8. Structure of itraconazole, ketoconazole and miconazole.

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