ASSESMENT OF FELODIPINE GLASS TRANSITION BEHAVIOUR USING MODULTED TEMPERATURE DIFFERENTIAL SCANNING CALORIMETRY

Natalija Zajc, Odon Planinšek, Stane Srčič*
Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, SI-1000 Ljubljana, Slovenia

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Abstract

Glassy felodipine samples have been investigated thermoanalytically by means of modulated temperature differential scanning calorimetry (MTDSC). The method advantage of improved signal to noise ratio is confirmed and the glass transition is determined independently from the relaxation phenomena. Experiments with linear saw-tooth modulation with different experimental parameters revealed the strong influence of the modulation period on the data derived. The activation energy of the felodipine glass transition is calculated, introducing different value as determined previously.
Key words: felodipine, glass transition, relaxation, experimental parameters

Introduction

Solubility has been a persistant problem in the development of pharmaceutical formulations. Since glasses and glassy mixtures have high energy levels, they are of interest in terms of enhancing dissolution rate and bioavailability. In a typical glassy state the molecular translation and rotation motions are drastically reduced.[1] Although having the structure of a liquid, the material has solid-like characteristics due to long structural relaxation times.[2] It is a non-equilibrium state, but the system is meta stable over a long period of time because of low rate of approaching the equilibrium. The viscosity usually exceed 10^{12} Pas.[3] Measuring a glass transition temperature (T_g) and heat capacity change (ΔC_p) contributes to the characterisation of such materials, providing practical information about mechanical properties, and physical and chemical stability.

A low molecular mass substance felodipine (M_r 384.3), a Ca^{2+} antagonist from the group of 1,4-dihydropyridines, is very slightly soluble in water.[4] Studies have been carried out to enrich the knowledge about glassy felodipine, using methods as DSC, FTIR, SEM, X-ray powder diffraction, pulse NMR spectroscopy and AFM.[5,6,7] However, using conventional DSC a glass transition determination may be difficult, because the change often occures over a wide temperature range. Quantification is

additionally disturbed by baseline curvature, low signal to noise ratio and the enthalpic relaxation endotherm, usually superimposed on the transition.[8] Modulated temperature DSC (MTDSC) is an extension of conventional DSC, that overcomes disadvantages of its precursor. The sample is subjected to a modulated temperature program, resulting in modulated sample response. More details on the principles of MTDSC can be found in a number of papers.[9,10,11] Dynamic DSC (DDSC) is a variety of MTDSC, employing a linear stepwise distortion of the temperature program. Mathematical treatment of the heat flow response yields a group of signals with specific information about material.[12] The important advantages of MTDSC over conventional DSC include higher resolution without loss of sensitivity, improved signal to noise ratio, reduced baseline curvature, the possibility of measuring heat capacities in a single run and the separation of overlapping thermal events.[9,13] The quality of the results depends on the operating variables.[14,15] The appropriate parameter choice is emphasized and the phase angle determination is addressed. In a search of optimal conditions for felodipine glass transition observation, the experimental parameters were varied individually.

Experimental

Materials

Felodipine was obtained from Luwitrade, Lichtenstein. The presence of two polymorphic modifications, designated as II and III,[6] was confirmed by conventional DSC measurement of felodipine as received (onset melting points 141.9 °C and 145.1 °C, respectively). Samples of approximately 4.5 ± 0.3 mg were non-hermetically encapsulated in Perkin-Elmer standard aluminum pans. The glassy state was prepared by heating the samples above the melting point, then allowed to cool spontaneously to room temperature.

Modulated temperature differential scanning calorimetry

MTDSC measurements were conducted on a Perkin-Elmer Pyris 1 power compensation DSC (Norwalk, CT, USA) with DDSC accessory, equipped with Intracooler 2P. For DDSC evaluation Pyris software (Perkin-Elmer) was used. The DSC cell was purged with dry nitrogen at a flow rate of 20 ml/min. Samples were run in the range from 30 °C to 70 °C with a linear, stepwise temperature change using heat-cool,

isothermal-heat or heat-only repetitive program steps, the type of the step being dependent on the combination of variables. The underlying heating rates between 0.5 and 5 °C/min were used with amplitude of temperature change ± 0.375 °C and modulation period of 60 s. When analyzing an influence of the modulation amplitudes in the range from ± 0.125 to ± 5 °C, underlying heating rate of 1 °C/min and 60 s period were used. The period of 30, 60 or 90 s was combined by modulation amplitude of ± 0.375 °C and heating rate of 1 °C/min. Each experiment was repeated at least three times. The empty pan was used as a reference pan, matching the sample pans as much as possible by mass (± 0.1 mg). For each experiment baseline subtraction was carried out, using the baseline with corresponding conditions. Values of ΔC_p and T_g were determined from the storage heat capacity (C_p'). T_g was determined as the temperature at which the heat capacity change is half the complete change.

Differential scanning calorimetry

A conventional DSC method was used with the same equipment for determining the purity of felodipine as received. For this purpose the samples were heated with linear program of temperature change from 30 °C to 150 °C using a heating rate of 10 °C/min at a nitrogen flow of 20 ml/min.

Calibration procedure

The instrument was calibrated for temperature and enthalpic response using indium standard. For heat capacity calibration the response of sapphire standard was compared to literature values in the felodipine glass transition region. The calibration was performed using the same underlying heating rate and the same pan type as in the experiments.

Results and discussion

Using conventional DSC the glass transition has been observed as a shift in the baseline of the heat flow. Because of unappropriate signal to noise ratio of the method, wrinkled DSC curve is produced (Figure 1), showing the glass transition, accompanied by relaxation endotherm. MTDSC uses the dynamic program with high heating rates in the heating parts, providing a larger dynamic effect for improved sensitivity while, at the

same time, a low underlying heating rate produces closely spaced data for better resolution. This results in effective extraction of the glass transition from other events which obscure it. In DDSC a heat-cool type of program is much more dynamic, making this type of the DDSC more appropriate for T_g analysis comparing to isothermal-heat or heat-only type. However in our case, to examine the influence of various values of the defined variable, isothermal-heat and heat-only modes were also employed. From the modulated heat flow, storage and loss heat capacity (C_p' and C_p", respectively) have been obtained (Figure 1). C_p' defines molecular motions within the sample, while C_p" displays the dissipative properties of the materials - it is an indication of the sample not responding instantaneously to the temperature change.[16]

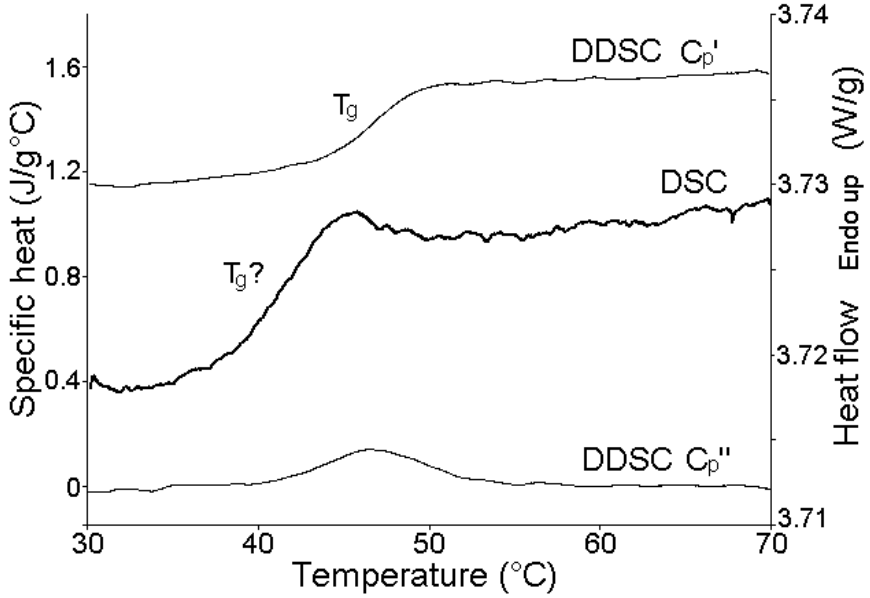

Fig. 1: Conventional DSC scan of glassy felodipine (DSC) in the glass transition region and its MTDSC response, representing the storage heat capacity (Cp') and loss heat capacity (C_p")

Similar to DSC curve glass transition appears on C_p' curve in a form of sinusoidal deviation, as seen on Figure 1. There is no evidence of relaxtion enthalpy. Relaxation phenomena is caused by prior thermal and mechanical history. The effect in the heating thermogram of conventional DSC is the recovery of the enthalpy lost during the ageing at temperatures below T_g. Storage and loss heat capacity curves are involved only in thermodynamically reversible processes. Owing to its irreversible nature, enthalpy relaxation is not revealed in C_p' or C_p". It has been established that both heat capacities

are unaffected by the ageing process and threfore analysing them it is impossible to determine the relaxation enthalpy.[17]

Comparing to conventional DSC, MTDSC is much more complicated, regarding the number of parameters employed. To get a quality response, the sample has to be treated in order to prevent formation of temperature gradients. Small sample masses of felodipine were used and the glassy samples were prepared by cooling spontaneously from the melt. We assumed that, on forming a thin glassy film, felodipine has evenly covered the bottom of the DSC aluminium pans, assuring adequate thermal contact between the sample and pan.

Table 1: Influence of MTDSC parameters on felodipine glass transition temperature (T_g) and heat capacity change (ΔC_p).
T_a: amplitude of temperature modulation, t_p: periode of modulation, UHR: underlying heating rate; each value represents a mean of 3 experiments ± S.D

MTDSC parameter	value of parameter	T_g (°C)	ΔC_p (J g^{-1} K^{-1})
heating rate (°C min^{-1})	0.5	45.2 ± 0.2	0.25 ± 0.01
	1	46.4 ± 0.2	0.26 ± 0.00
T_a ± 0.375 °C	2	45.6 ± 0.1	0.27 ± 0.02
t_p 60 s	5	45.9 ± 0.3	0.31 ± 0.01
amplitude (°C)	± 0.125	46.8 ± 0.3	0.30 ± 0.01
	± 0.25	46.8 ± 0.3	0.29 ± 0.04
	± 0.5	46.6 ± 0.1	0.30 ± 0.01
	± 1	46.6 ± 0.1	0.29 ± 0.02
	± 2.5	46.6 ± 0.0	0.27 ± 0.03
UHR 1 °C/min	± 5	46.1 ± 0.2	0.27 ± 0.02
t_p 60 s			
period (s)	30	47.9 ± 0.1	0.29 ± 0.01
	60	46.5 ± 0.0	0,30 ± 0.01
T_a ± 0.375 °C	90	45.6 ± 0.0	0.35 ± 0.01
UHR 1 °C/min			

In modifying the underlying heating rate (UHR), values of 0.5, 1, 2 and 5 °C/min were chosen. A distinct step change of the baseline, observed on the storage heat capacity, was quantified. When using conventional DSC an increase of T_g with increase of heating rate is noticed.[1] Using MTDSC we perceived no significant difference

between the glass transition temperatures of felodipine (45.8 ± 0.5 °C), obtained at various heating rates (Table 1).

The dynamic effect of the modulated program was the same in all cases. The magnitude of the heat capacity change was slightly increased with underlying heating rate. The relative standard deviation is approximately 9.5%. Taking levels of 0.05 as indicative of significant differences it has been shown statistically that the discrepancies are out of the range of experimental error. However, this may simply be a manifestation of increased sensitivity caused by growing underlying heating rate. With values of 2 and 5 °C/min, five or less modulations occur during the glass transition. For adequate software calculation it is necessary to ensure at least six modulations through any transition in order to obtain characteristic heat capacity components, hence low underlying heating rates are essential.[15]

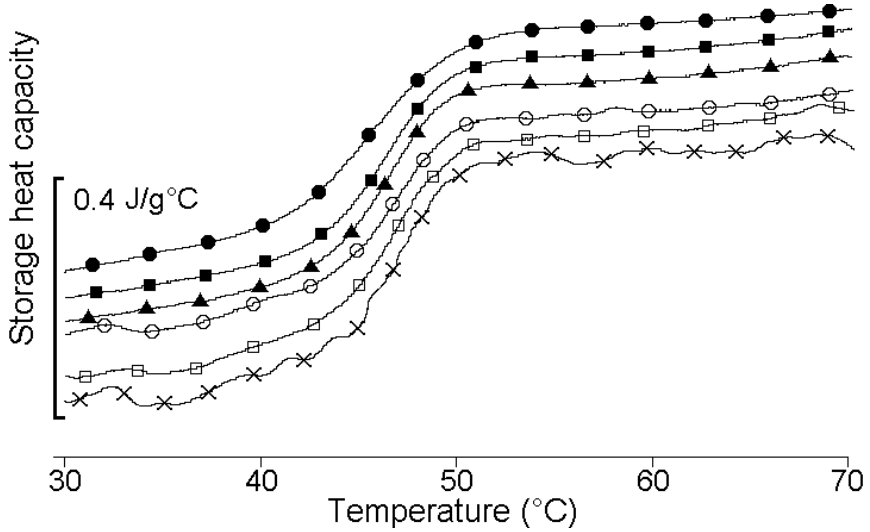

Fig. 2: Storage heat capacity of felodipine in the glass tansition region using different values of temperature amplitude: ± 5 °C (●); ± 2.5 °C (■); ± 1 °C (▲); ± 0.5 °C (○); ± 0.25 °C (□); ± 0.125 °C (x)

The maximum amplitude of temperature program (T_a) is dependent on the rate of heat capacity change. In the case of a glass transition it is possible to use amplitudes of more than 1 °C.[18] However, the amplitude is limited by heat transfer into the furnaces and the sample, so that the choice of this parameter should tend towards sufficiently small values, in our case between ± 0.125 and ± 5 °C. It is important to note, that power compensation DSC has been used, where individual heaters are closer to the sample and

temperature sensor, hence the thermal response should be faster than in the case of heat flux DSC. Table 1 lists the T_g and ΔC_p values for the MTDSC analysis of felodipine at different amplitudes. It is evident that there is no major effect on the glass transition parameters. The mean values, with standard deviation, of the glass transition temperature and heat capacity change are 46.6 ± 0.3 °C and 0.29 ± 0.02 J/gK, respectively. This can also be confirmed by inspection of Figure 2, where the storage heat capacity in the glass transition region at various amplitudes is shown. With increase of amplitude the signal to noise ratio is distinctly improved.

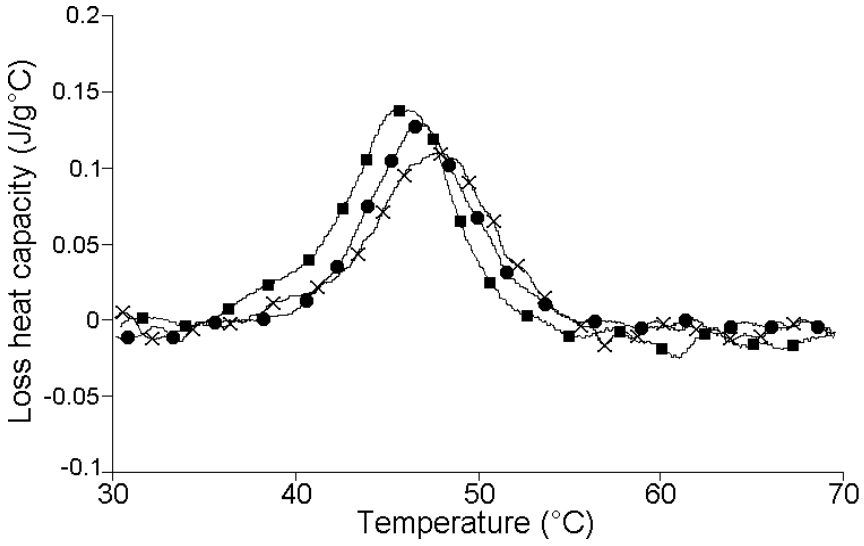

Fig. 3: Loss heat capacity of felodipine in the glass transition region using a modulation period of 90 s (■), 60 s (●) or 30 s (x)

The influence of period (t_p) was investigated too. Increasing the period from 30 to 90 s slightly decreased the T_g. This is to be expected because C' and C'' are frequency dependent.[12] Figure 3 demonstrates the peak of the loss signal in the glass transition region. The maximum temperature of the peak coincides with T_g from storage curve. Construction of the activation diagram clearly demonstrates the frequency (reciprocity of period) dependence of T_g for felodipine (Figure 4).

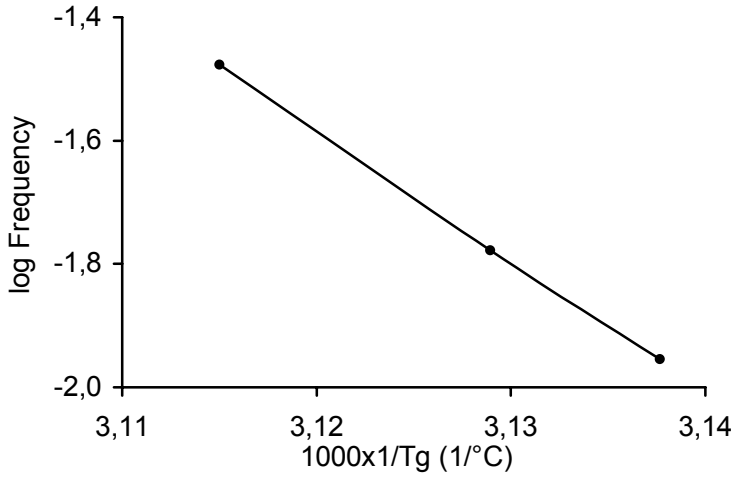

Fig. 4: Activation diagram of the glass transition of felodipine

From the slope of the curve the activation energy can be calculated, which, in the case of the felodipine glass transition, is 175.4 kJ/mol. The value differs from previously reported 132.7 kJ/mol.[5] Generally, for modulation period the use of 60 s is recommended when using standard aluminum pans and nitrogen purge gas.[4]

The tangent delta curve is derived as the ratio of loss and storage signals. In the region of the glass transition of the felodipine a clear peak is observed which indicates increased movement of molecules (Figure 5).

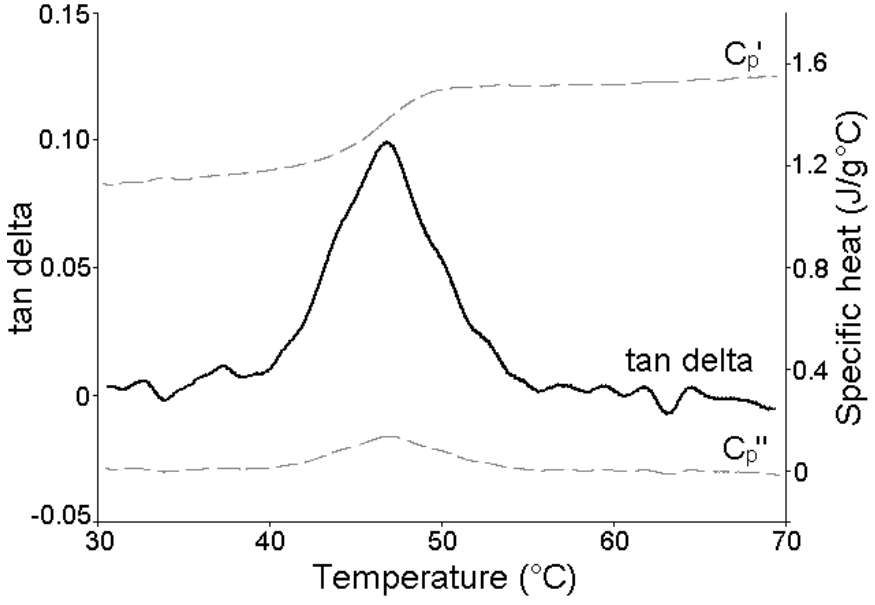

Fig. 5: Tangent delta curve as the ratio between loss and storage curve in the glass transition region of felodipine

Our experiments are in good agreement with previous studies concerning the MTDSC evaluation of T_g.[18] However; the problem of examination of the relaxation process bound to the glass transition still remains. The irreversible part of the process can be calculated as the difference between the total component (approximately the same as conventional DSC response) and the reversible storage component (C_p').[17] It is evident from the Figure 6, that analysis of irreversible C_p offers the study of relaxation phenomena.

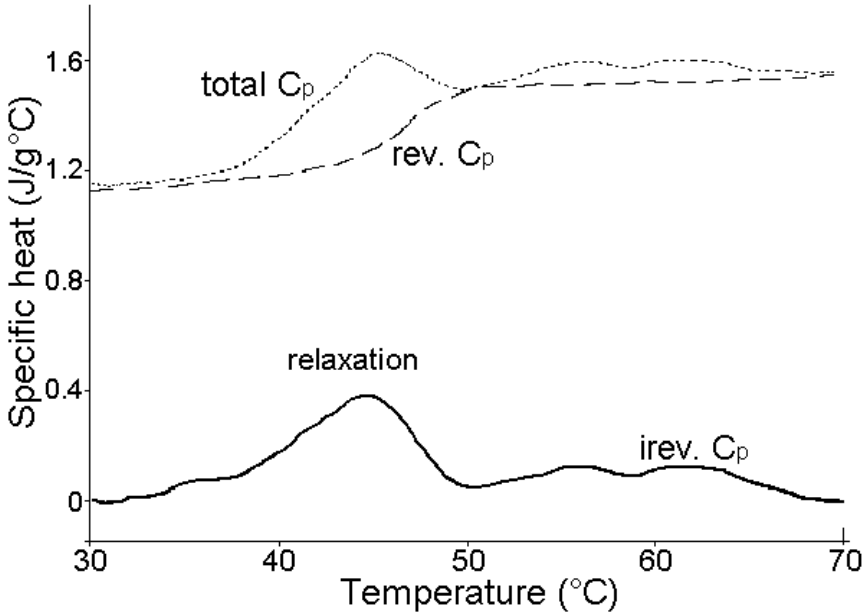

Fig. 6: Felodipine total heat capacity, reversible (storage) component and ireversible component in the glass transition region

Conclusions

MTDSC has been confirmed as a useful method for precise characterization of glass transition phenomena of an amorphous drug substance. The influence of experimental parameters on T_g and ΔC_p estimation can be investigated unambiguously owing to the improvement of signal to noise ratio and the separation of the glass transition from other co-existing events such as enthalpy effects caused by prior thermal and mechanical history.

Results support some previous findings about the impact of the MTDSC variables on T_g determination in the case of low molecular mass drugs. In particular, a careful choice of modulation period must be carried out, since the storage and loss heat capacity

are frequency dependent. Taking into account all the points mentioned above, the glass transition temperature and heat capacity change could be correctly quantified.

The conclusions of this study may also be relevant to glass transition determination for other amorphous systems such as drugs and polymeric excipients, spray and freeze dried materials.

References and Notes

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Povzetek

Steklasti felodipin smo termoanalitsko preiskovali z dinamično diferenčno kalorimetrijo z modulacijo temperature (MTDSC). Potrdili smo izboljšano razmerje signal/šum kot prednost metode ter ovrednotili steklast prehod neodvisno od relaksacije. Meritve z linearno zobato modulacijo pri različnih eksperimentalnih spremenljivkah pokažejo močan vpliv periode modulacije na rezultate. Izračunali smo aktivacijsko energijo steklastega prehoda felodipina, ki pa se razlikuje od do sedaj znanih vrednosti.