

## Molecular Mobility of the Paracetamol Amorphous Form

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The purpose of this paper is to study the molecular mobility of paracetamol molecules in their amorphous state below the glass transition temperature ( $T_g$ ) in order to evaluate the thermodynamic driving force which allows the amorphous form to recrystallize under different polymorphic modifications. Samples were aged at temperatures of  $-15$ ,  $0$ ,  $6$ , and  $12$  °C for periods of time from 1 h to a maximum of 360 h. The extent of physical aging was measured by a DSC study of enthalpy recovery in the glass transition region. The onset temperature of glass transition was also determined ( $T_g$ ). Enthalpy recovery ( $\Delta H$ ) and change in heat capacity ( $\Delta C_p$ ) were used to calculate the mean molecular relaxation time constant ( $\tau$ ) using the empirical Kohlrausch–Williams–Watts (KWW) equation. Enthalpy recovery and onset glass transition temperature increased gradually with aging and aging temperatures. Structural equilibrium was reached experimentally only at an aging temperature of  $12$  °C ( $T_g - 10$  °C), according to the  $\Delta H_\infty$  results. The experimental model used is appropriate only at lower aging temperatures, while at higher ones the complexity of the system increases and molecular polymorphic arrangement could be involved. When structural equilibrium is experimentally reached, molecules can be arranged in their lowest energy state, and the polymorphic form I formation is the one preferred.

**Key words** paracetamol; polymorphism; amorphous form; molecular mobility

A previous paper<sup>1)</sup> described the interesting use in direct compression of tablets of the paracetamol orthorhombic form II. It was also pointed out that compressibility decreases by increasing form I content. The typical molecular arrangement of form II is responsible for crystal plastic deformation under compression. In fact, the orthorhombic crystalline structure is constituted by parallel planes characterized by high molecular density and by weak interplane bonds which, under compression, behave like sliding planes, causing plastic deformation.<sup>2)</sup>

The orthorhombic form II was obtained in our laboratory by a melting method. DSC studies pointed out that the obtained crystal form depends on both the cooling rate of the melt and the crystallization conditions of the amorphous form.<sup>3)</sup> However, during laboratory scale-up,<sup>3)</sup> we observed some anomalies on the differential scanning calorimetry (DSC) thermograms of the obtained form. In fact, although the X-ray diffraction patterns undoubtedly showed the presence of a pure form II (method sensibility  $>2\%$ ), DSC thermograms evidenced the melting endotherm of form I preceded by a melting endotherm of form II. In order to interpret this unusual behaviour, in this work we assume an incomplete recrystallization of the amorphous material during the scale-up procedure. After quench cooling to room temperature of the melt, the amorphous material recrystallizes within 2 h almost completely in polymorphic form II. It could be that, owing to the greater mass involved in the scale-up than that in DSC experiments, not all the amorphous form recrystallizes and its behaviour could be similar to that of an aged material. The possibility to evidence the presence of a low amount of this amorphous form by an X-ray diffraction dosage was not satisfied. So we decided to study, by isothermal experiments of physical aging, the molecular mobility of the amorphous form to understand its thermodynamic tendency to be transformed towards one polymorphic form.<sup>4)</sup>

### Experimental

Paracetamol monoclinic form F.U.-B.P. (A.C.E.F., Italy) was melted in a

30- $\mu$ l aluminium DSC pan. Different cooling rates were applied ( $10$  °C/min or  $200$  °C/min). For aging studies, the amorphous form was supercooled to  $T_a$  (aging temperature) conditions of  $-15$ ,  $0$ ,  $6$ , and  $12$  °C at a cooling rate of  $200$  °C/min.

Samples were analyzed using a DSC (Pyris 1, Perkin Elmer, U.S.A.) equipped with an ethanol cooling system circulating in a refrigerator (Cryostat F4-Q, Haake Q, Germany). A dry purge of nitrogen gas ( $20$  ml/min) was employed for all runs. The DSC was calibrated for temperature and heat flow using pure samples of indium and zinc standards, and frequent calibration checks were made. Precautions were taken to minimize the interfering effect of sample mass, thermal contact, and heat transfer lags. Sample masses were therefore varied only between 3 and 4 mg, samples were laid in the aluminium pan in a constant thin layer, and aluminium pans were always of the same type. The paracetamol crystals were melted in the aluminium pan at  $180$  °C ( $T_m = 169$  °C for the marketed form) and kept at this temperature for 5 min to avoid incomplete melting. The liquid was supercooled at a rate of  $200$  °C/min to  $T_0$ , that was  $5$  °C less than  $T_a$ . A second heating run ( $10$  °C/min) was performed to reach the aging temperature ( $T_a$ ). Samples were kept at  $-15$ ,  $0$ ,  $6$ , and  $12$  °C for 1, 3, 6, 24, 48, 72, 168, 264, and 360 h. They were then cooled again at  $T_0$  and then reheated ( $10$  °C/min) through their  $T_g$  to measure the enthalpy recovery ( $\Delta H$ ). An outline of this procedure is shown in Fig. 1. After different aging times ( $t_a$ ), a second heating run was performed to  $T_m$  at a heating rate of  $10$  °C. A cycle for an unaged sample was also run. After the melting and cooling steps, a second heating run was carried out immediately without any isothermal aging step. Any thermal processes like glass transition and melting were then recorded. In particular, around the glass transition zone, the onset glass transition temperature ( $T_g$ ),

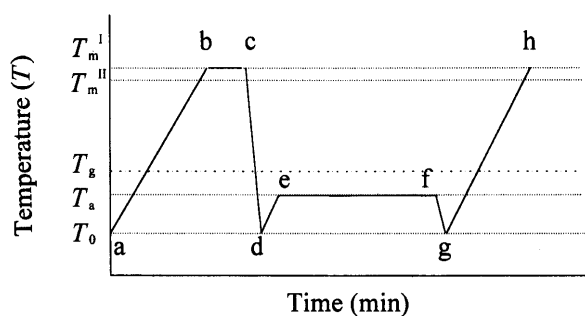


Fig. 1. Temperature Program to Which Samples Were Subjected

$T_0$  is a temperature below  $T_a$ , the aging temperature;  $T_g$  is the glass transition temperature;  $T_m^I$  is the melting temperature of monoclinic form I;  $T_m^II$  is the melting temperature of the orthorhombic form II. ab: heating to melting temperature at  $10$  °C/min; bc: isothermal step to complete the melting; cd: quenching to  $T_0$  at  $200$  °C/min; de: heating to  $T_a$  at  $10$  °C/min; ef: aging period; fg: cooling to  $T_0$  at  $10$  °C/min; gh: second heating to  $T_m$  at  $10$  °C/min.

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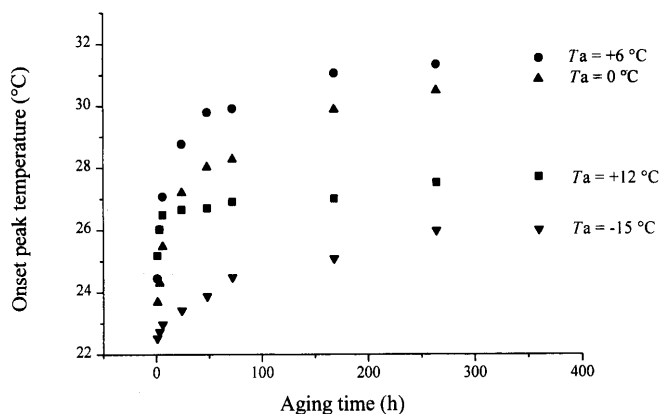


Fig. 2. Onset Peak Temperatures in the Glass Transition Region Plotted versus Aging Time for All Aging Temperatures

Table 1. Physico-Chemical Properties of Paracetamol

Molecular weight/amu	151.16	
Glass transition temperature/°C	22.63 <sup>a)</sup>	
Melting temperature/°C	Form II	Form I
	158	169
$(T_m/K)/(T_g/K)$	$T_m^{II}/T_g$	$T_m^I/T_g$
	1.458	1.495
Change in heat capacity at $T_g$ ( $\Delta Cp$ )/(J/g·°C)	0.6	

a) Determined from an unaged sample.

change in heat capacity ( $\Delta Cp$ ), and enthalpy recovery ( $\Delta H$ ) were calculated. This recovery was calculated from the peak area between the DSC curve of the aged sample and that of the extrapolated supercooled-liquid baseline. Because the experimental glass transition temperature of the materials varied according to the preparation conditions of the glassy material (cooling conditions) and according to the  $T_g$  measurements (heating conditions), particular care was taken to standardize the whole procedure.<sup>5)</sup> Around the melting process, the onset temperature was measured. The mean values of each parameter were determined from replicate samples.

## Results and Discussion

The paracetamol amorphous form is obtained by quench cooling (200 °C/min) of the melt, while its slow cooling (10 °C/min) leads to the crystallization as form I already during cooling. When the amorphous form is kept at a temperature higher than  $T_g$ , crystallization as form II occurs spontaneously, at the most within 2 h, while if the amorphous form is kept at temperatures below the  $T_g$ , crystallization does not occur spontaneously. However, crystallization of the amorphous form is promoted by a new reheating and according to the heating rate: a relatively fast heating rate (10 °C/min) gives form II, while a very slow one (0.01 °C/min) gives form I.

The physico-chemical properties of paracetamol are presented in Table 1. The  $T_g$  of an unaged sample is 22.63 °C. When the amorphous form is aged at temperatures below  $T_g$ , DSC scan shows the presence of an endothermic relaxation peak which is dependent on temperature and aging time and is related to the spontaneous losses in enthalpy of the amorphous materials during storage, due either to the normal molecular motions occurring under those conditions, or to the thermodynamic driving force towards a more stable crystalline state. In a glassy material, the rate of enthalpy loss can be considered to reflect the level of molecular mobility in the

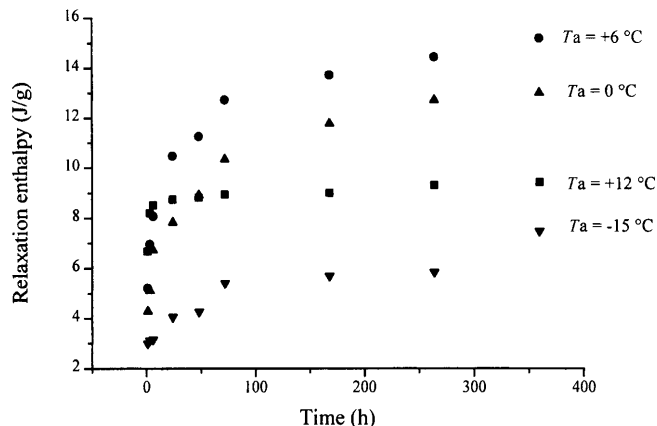


Fig. 3. Relaxation Enthalpies Plotted versus Time for All Aging Temperatures

non-equilibrium glassy amorphous sample. Upon reheating the "aged" glassy material, the enthalpy loss is fully recovered at or near  $T_g$  and can be very easily quantified using standard thermoanalytical techniques such as DSC.<sup>6)</sup>

From our experiments, it could be observed that the position of the endothermic peak at the glass transition varies with varying aging times and temperatures (Fig. 2): it increases with aging time and temperature except for a  $T_a$  of 12 °C, which is near that of  $T_g$ .

From  $T_g$  it is possible to calculate a limiting value,  $\Delta H$ , at which structural equilibrium is reached, at a rate depending on aging time and temperature. A limit relaxation enthalpy  $\Delta H$ , whose value increases with rising aging temperature, must correspond to each  $T_a$ . According to Bauwens-Crowet and Bauwens<sup>7)</sup> and Kemmish and Hay,<sup>8)</sup> who assumed that  $\Delta Cp$  is independent of temperature, the  $\Delta H$  value can be determined from the equation

$$\Delta H_{\infty} = (T_g - T_a) \cdot \Delta Cp \quad (1)$$

where  $T_g$  is the glass transition temperature,  $T_a$  is the experimental temperature, and  $\Delta Cp$  is the change in heat capacity at  $T_g$ . In our studies,  $\Delta Cp$  was determined by averaging values from all the experiments. No relationship was found between  $\Delta Cp$  and the experimental conditions ( $T_a, t_a$ ). In Fig. 3, it can be observed that, with the exception of  $T_a$  12 °C, enthalpy relaxation increased gradually with aging time according to the aging temperature. At 12 °C,  $\Delta H$  became practically constant after about 24 h, an aging period sufficient to let the sample reach its structural equilibrium state. Our results confirm that the limiting enthalpy relaxation can only be found experimentally when  $T_a$  is close to  $T_g$ , not more than approximately  $T_g - 15$  °C.<sup>5)</sup>

Some models connect the enthalpy recovery data with molecular parameters such as relaxation time. Even if each molecular motion (responsible for structural modification) shows its due characteristic time constant, the most widely used models are defined in accordance with a mean relaxation time for all the molecular motions (vibrational, rotational, etc.). The most widely used approach is based on the empirical Williams-Watts equation, which was originally developed for describing dielectric relaxation data.<sup>9)</sup> From the maximum enthalpy recovery  $\Delta H$  calculated from Eq. 1, it is possible to calculate the extent to which a material relaxes ( $\phi$ ) under any given conditions of time ( $t$ ) and temperature

Table 2. Results for the Best Fit to Eq. 3

Aging temperature/°C	$\beta$ value	$r$	Mean molecular relaxation time $\tau$ /h
-15	0.4—0.5	-0.96	90.91
0	0.1—0.2	-0.99	8.62
6	0.8	-0.97	32.26
12	—	—	—

( $T$ ):

$$\phi_t = 1 - (\Delta H_t / \Delta H_\infty) \quad (2)$$

where  $\Delta H_t$  is the measured enthalpy recovery under those conditions. The temperature dependence of enthalpy relaxation can be considered in terms of the mean relaxation time  $\tau$ :

$$\phi_t = \exp(-t/\tau)^\beta \quad (3)$$

where  $\tau$  is the mean molecular relaxation time,  $t$  is the time, and  $\beta$  is a constant. Typically it is assumed that there are multiple relaxation processes with a distribution of relaxation times.  $\beta$  is a relaxation time distribution parameter with a value ranging from 0 to 1 and, if  $\beta$  is equal to unity, there is a single relaxation time and the data can be described using a simple single relaxation time model.

Generally, the  $\beta$  value varies according to the chemical structure of the molecule involved, but it is generally reported to have only slight variations with temperature.<sup>8)</sup> In our case,  $\beta$  shows a certain reduction with increasing temperature from -15 to 0, but an inversion when temperature is further increased.  $\beta$  has also been shown to correspond to the strength/fragility of the material but, in our study, with regard to the discontinuity exhibited by the  $\beta$  value, no definite conclusion is possible.

The best fit for the aging data is obtained using a linear regression between “ $\ln \phi$ ” and “time.” Results are presented in Table 2. This model seems appropriate for aging temperatures in the range from -15 °C to 0 °C, where the mean molecular relaxation time decreases with increasing aging temperature, which is physically congruent. At those temperatures, a relatively narrow molecular distribution process can be presumed. For an aging temperature of 6 °C, the mean molecular relaxation time increases in comparison with 0 °C. It is thus possible that the system acquires a new molecular package which relaxes according to a new mean relaxation time. At an aging temperature of 12 °C, a best fit to the equation has not been found. It is possible that, at low temperatures, far enough from the glass transition temperature and experimentally distant from the equilibrium state, the limited molecular freedom gives a simple relaxation process, which is expressed appropriately by Eq. 3, whereas with increasing temperature, in the region close to the glass transition temperature and to the equilibrium state, activation of molecular motions increases the complexity of the relaxation process, and the model is no longer suitable. Actually, polymorphic arrangements could be involved in the glass system, in particular at higher temperatures, at which the probability of molecules being arranged in their lowest energy state is highest. When paracetamol samples aged at aging temperatures of -15, 0, and 6 °C are reheated up through their  $T_g$  to the  $T_m$ , a thermogram represented in Fig. 4 is recorded; after the

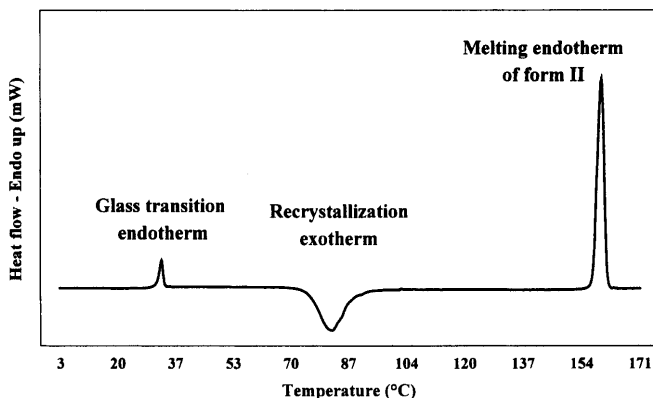


Fig. 4. Paracetamol Thermogram for the Second Heating Run After an Aging Time of 15 d at 6 °C

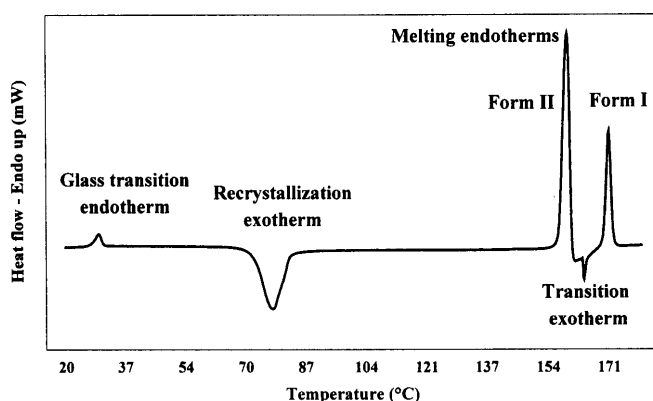


Fig. 5. Paracetamol Thermogram for the Second Heating Run After an Aging Time of 7 d at 12 °C

glass transition region, the crystallization exotherm and a melting temperature of about 158 °C can then be observed, corresponding to the melting temperature of the orthorhombic form II. On the other hand, during the second heating of a sample aged at a temperature of 12 °C for a time greater than 24 h, in addition to the glass transition endotherm and the recrystallization exotherm, a first endothermic peak corresponding to the melting of polymorphic form II can be observed; this was followed by the exotherm of crystallization of form I and the endotherm of melting of polymorphic form I (Fig. 5). At that aging temperature and time, the samples reached their equilibrium state and paracetamol molecules could arrange themselves to give the more stable monoclinic form I.

During the scale-up an incomplete crystallization of the melt at room conditions could be possible. This amorphous form, at temperatures very near  $T_g$  can in a short time attain its structural equilibrium and recrystallize under the more stable form I, which thus co-exists with form II.

## Conclusion

The enthalpy relaxation of the paracetamol amorphous state has been studied below  $T_g$  under several aging conditions. From this study, it can be noted that structural equilibrium was experimentally reached only after 24 h, at an aging temperature of 12 °C, a temperature which is near that of  $T_g$ . At an aging temperature of 6 °C, the experimental aging time was not long enough to reach the structural equilibrium. Ap-

plication of the Kohlrausch–Williams–Watts (KWW) equation allows us to calculate the molecular relaxation time constant, whereby it is found that the mean relaxation rate of molecular motion increases with increasing aging temperatures ( $-15^{\circ}\text{C}$ ,  $0^{\circ}\text{C}$ ). Nevertheless, at higher temperatures, when the system approaches its structural equilibrium, the experimental model is no longer appropriate for describing the complexity of the system. When structural equilibrium is reached, the probability that molecules are arranged in their lower energy content increases and the crystallization of the amorphous form on the stable monoclinic form I is favored, simultaneously with crystallization of the orthorhombic form II.

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