Thermal Properties and Stability of Glassy Tri-*O*-methyl-β-cyclodextrin[1)]

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Glassy tri-*O*-methyl-β-cyclodextrin (TMCD) was prepared by cooling the melt and the glassy state was confirmed by measuring the glass transition temperature (T_g) and the anomalous endothermic peak (heat capacity maximum) on a differential scanning calorimetry (DSC) curve. Glassy TMCD showed a glass transition at 356 K and an anomalous endothermic peak. The value of the ratio of T_g and the melting temperature (T_m) of TMCD was 0.83. The influence of the heating rate of the glass prepared at the cooling rate of −1.25 K/min on the glass transition was examined, and the apparent activation energy of glass transition was calculated to be 223.4 kJ/mol. The rate and quantity of relaxation of glass was determined by the area under the anomalous endothermic peak of the DSC curves of glasses prepared at various cooling rates, that of glassy TMCD was found to be extremely large. Enthalpy relaxation during the isothermal aging of glassy TMCD occurred most remarkably at 341 K. Devitrification of glassy TMCD did not occur for more than 1.5 years at 25 °C. Pulverized glassy TMCD remained as glass for 1 year. Glassy TMCD was very stable and TMCD was found to be a good glass-former.

Key words tri-*O*-methyl-β-cyclodextrin; glass transition temperature; differential scanning calorimetry; X-ray analysis

In recent years, Tsukushi *et al.*[2)] reported that the melt of tri-*O*-methyl-β-cyclodextorin (TMCD) was easily undercooled to form a glassy state, and the liquid-quenched glass (glassy TMCD) showed a glass transition at 77.8 °C (350.8 K). From a thermodynamic point of view, the molar heat capacities and the relaxation processes of the ground amorphous solid and liquid-quenched glass were investigated by a low temperature adiabatic calorimeter.[2)] However, the thermal properties of glassy TMCD, such as the influences of the cooling rate of the melt, the heating rate of the glass on the glass transition, and the isothermal aging process below T_g on the glassy state, have not been studied by thermal analysis.

In the present paper, glassy TMCD was prepared by cooling the melt, and the glassy state was confirmed by the detection of a jump in heat capacity and an anomalous endothermic peak on the differential scanning calorimetry (DSC) curve. The isothermal enthalpy relaxation process of the glass below T_g was studied by thermal analysis. The influence of cooling rates and heating rates on the relaxation of glassy TMCD was investigated. The effect of pulverization on the stability of glassy TMCD was investigated.

Thermal properties and the stability of glassy TMCD were compared with those of glassy pharmaceuticals previously reported.[3)]

Experimental

Materials TMCD was purchased from Toshin Chemical Co., Ltd.

Preparation of Glass The glass was prepared in the same way as reported previously.[3)] Crystals of TMCD were melted in an aluminium sample pan equipped with an Intracooler I system, and the melts were solidified by cooling them to 290 K at various rates. For stability studies, the crystals were melted by heating with a mantle heater and the melts were solidified by allowing them to cool to room temperature on standing.

X-Ray Diffraction Studies (Powder Method) X-ray diffraction patterns were measured as reported in the previous paper.[3)] A Rigaku Denki Geigerflex instrument equipped with a scintillation counter as a detector was used for these studies. Every experiment was carried out under the following conditions: target, Cu; filter, Ni; voltage, 35 kV; current, 15 mA; receiving slit, 0.3 mm; time constant, 1—5 s; scanning speed, 0.5—2°/min.

Thermal Analysis A Perkin Elmer DSC-2 differential scanning calorimeter equipped with an Intracooler I system was used. Measurement conditions were the same as those reported previously,[3)] as was the determination of the area under the anomalous endothermic peak.

Results and Discussion

1) Confirmation of the Amorphous State of the Solidified Melt by the X-Ray Diffraction Method Figure 1 shows the powder X-ray diffraction pattern of crystal and the solidified melt of TMCD. The solidified melt was a transparent glassy mass. A halo was observed in the diffraction pattern, and the solidified melt was in an amorphous state.

2) Glass Transition Temperature and T_g/T_m of Glassy TMCD The DSC results are shown in Fig. 2. The DSC curve of the crystalline TMCD showed an endothermic peak at 429 K due to the melting. The melt was rapidly cooled to 290 K and reheated. The heating rate of 40 K/min was adopted to observe T_g and the anomalous endothermic peak. Glassy TMCD showed a glass transition at 356 K and an anomalous endothermic peak. The value of the ratio of T_g and melting temperature (T_m) was 0.83.

It has been reported[3c)] that the T_g/T_m values for a number of glassy pharmaceuticals lie between 0.65 and 0.80.

Murthy *et al.* reported that the T_g/T_m values for organic liquids are between 0.52 and 0.74.[4)] Yamaguchi *et al.*[5)] also reported that the T_g/T_m values for the macrolide compounds are between 0.72 and 0.89. Masumoto reported an evaluation of glass forming ability by using the critical cooling rate.[6)] He reported that as the T_g/T_m value was large, the amorphous phase was easily formed. Greer[7)] described that glass formation was expected to be easiest when the interval between the liquids (T_m) and the glass transition (T_g) was minimal. The T_g/T_m is a useful guide for predicting glass-forming ability. TMCD had a comparatively large T_g/T_m value of 0.83. It was found that TMCD has high glass-forming ability.

3) Influence of Heating Rate on Glass Transition The influence of the heating rate of glassy TMCD on glass

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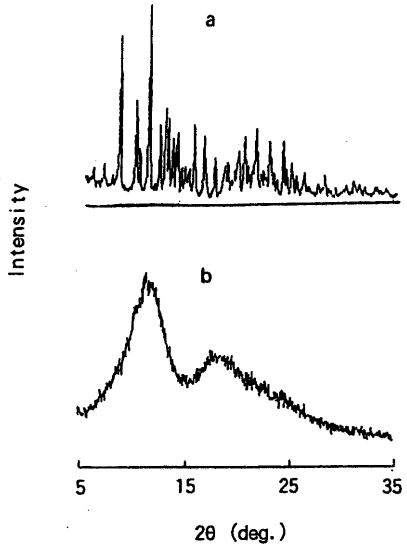

Fig. 1. X-Ray Diffraction Patterns of Crystal and Glass of TMCD
a, crystal; b, glass.

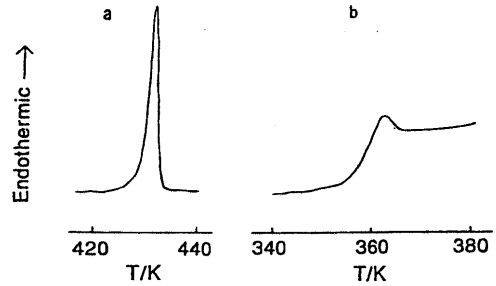

Fig. 2. DSC Curves of Crystal and Glass of TMCD
a, crystal: heating rate 10 K/min; b, glass: heating rate 40 K/min.

transition was examined. In previous papers,[3a,c] measurements were made at heating rates ranging from 2.5 to 40 K/min.

In the present study, no distinct glass transition was observed in the DSC curves with heating rates of 2.5 and 5 K/min of glassy TMCD prepared at quenching. Also, in the case of glassy TMCD prepared at a cooling rate of -1.25 K/min, no distinct glass transition was observed when measurement was carried out with a slow heating rate of 2.5 K/min. These results indicate that recovering the enthalpy of relaxation takes place during heating at a slow heating rate.[3a]

Therefore, to prevent the glass from recovering the enthalpy of relaxation during heating, the influence of the heating rate of glassy TMCD prepared at a cooling rate of -1.25 K/min on glass transition was examined at heating rates ranging from 5 to 40 K/min. The DSC curves are shown in Fig. 3.

The glass showed different DSC curves due to structural relaxation during continuous heating at different heating rates. Studies on the effect of the heating rate on T_g and the area under the anomalous endothermic peak revealed that the T_g and area under the anomalous endothermic peak increased as the heating rate increased.

A linear relationship was observed when the logarithm of the heating rate was plotted against $1/T_g$ (Fig. 4).

The apparent activation energy of the glass transition

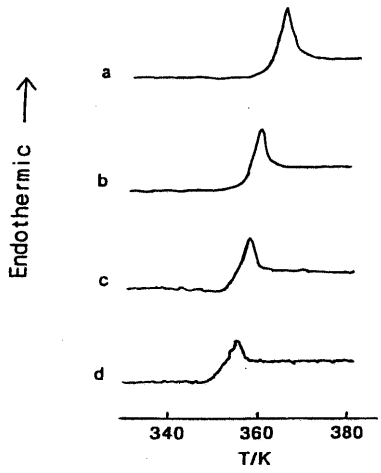

Fig. 3. Influence of Heating Rate on the DSC Curves of Glassy TMCD Prepared at the Cooling Rate of -1.25 K/min
Heating rates: a, 40; b, 20; c, 10; d, 5 K/min.

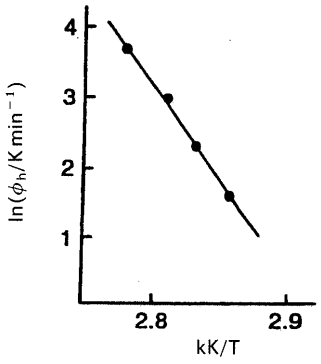

Fig. 4. Plot of $\ln \phi_h$ *vs.* $1/T_g$
ϕ_h: heating rate.

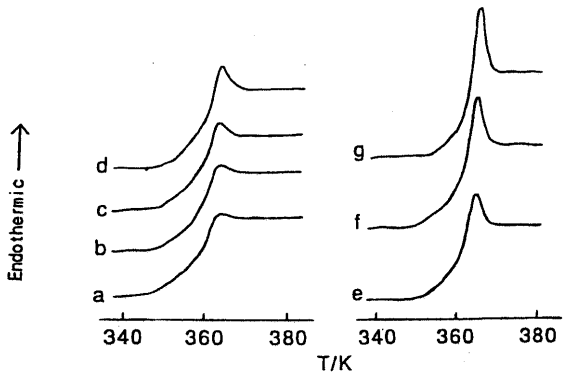

Fig. 5. DSC Curves at a Heating Rate of 40 K/min of Glassy TMCD Prepared at Various Cooling Rates
a, quenching; b, -20; c, -10; d, -5; e, -2.5; f, -1.25; g, -0.62 K/min.

of TMCD was calculated to be 223.4 kJ/mol according to an equation derived by Barton.[8]

From the result for TMCD and four pharmaceutical samples previously reported,[3c] it seems that the apparent activation energy of glass transition depends on T_g.

4) Relaxation of Glass during Preparation at Various Cooling Rates It is generally accepted that glass formation depends on the cooling rate of the melt. Also, in the case of pharmaceuticals, it has been recognized that the T_g of the glass formed increases and the anomalous

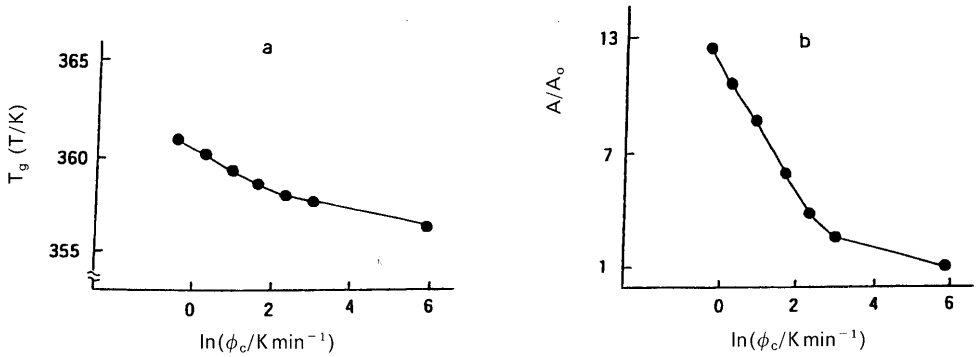

Fig. 6. Influence of Cooling Rate on T_g and the Area under the Anomalous Endothermic Peak

a, T_g; b, A/A_0; ϕ_c, cooling rate.

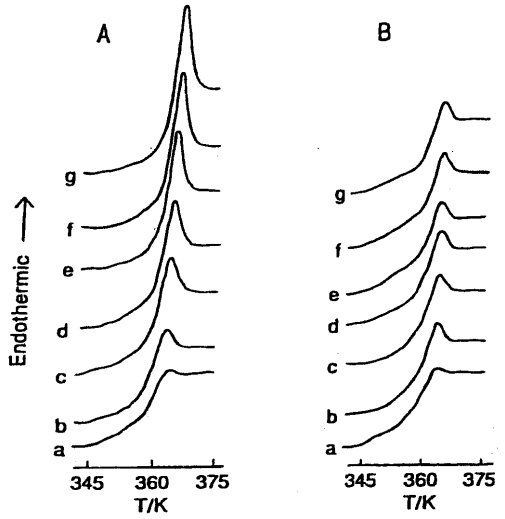

Fig. 7. Influence of Isothermal Aging at 341 and 351 K on the Area under the Anomalous Endothermic Peak of the DSC Curve

A, 341 K; B, 351 K; aging time: a, 0; b, 5; c, 10; d, 20; e, 30; f, 45; g, 60 min.

endothermic peak increases as well with a decrease in the cooling rate of the melt.[3a,c] Relaxation of the glassy TMCD during preparation at various cooling rates was studied. To examine the influence of the cooling rate on glass formation, the melt was cooled to 290 K below T_g at various cooling rates, and the glasses thus obtained were reheated to above T_g.

Measurements were made at a heating rate of 40 K/min. Figure 5 shows the DSC curves of glassy TMCD prepared at various cooling rates.

T_g increased, and the anomalous endothermic peak became larger with a decrease in the cooling rate of the melts. This indicates that relaxation takes place during cooling.

Figure 6 shows the influence of the cooling rate on T_g and the area under the anomalous endothermic peak of glassy TMCD.

The T_g of glassy TMCD varied, from 356 K in the case of quenching to 361 K in the case of a cooling rate of -0.62 K/min, as shown in Fig. 6a. The areas under the anomalous endothermic peak of the DSC curve of glass prepared at each cooling rate and quenching are denoted by A and A_0, respectively. To examine the rate and quantity of relaxation during cooling, A/A_0 was plotted against the logarithm of the cooling rate (Fig. 6b). A/A_0 increased as the cooling rate decreased. The influence of the cooling rate during glass preparation on the glass transition of glassy TMCD was similar to that of glassy pharmaceuticals previously reported.[3a,c]

A/A_0 of TMCD at every cooling rate was larger than that of the glassy pharmaceuticals.[3c] The rate and quantity of relaxation of glassy TMCD was found to be extremely large.

This indicates that stabilization by enthalpy relaxation of glassy TMCD occurs very readily during cooling. This phenomenon may be explained by TMCD having weak intermolecular interaction.[2]

5) Influence of Isothermal Aging Process below T_g on the Glassy State The influence of the isothermal aging process below T_g on the glassy state was examined. After the melt was rapidly cooled to a specified temperature below T_g in the region of 336—351 K, the sample was kept at a constant temperature to trace the isothermal relaxation process.

Figure 7 shows the influence of the isothermal aging process on the area under the anomalous endothermic peak of the DSC curves at 341 and 351 K.

At 341 K, T_g and the area under the anomalous endothermic peak increased with aging time, showing that the enthalpy relaxation proceeded gradually during standing at a temperature below T_g. On the other hand, at 351 K, the increase in the area under the anomalous endothermic peak and T_g was only slightly observed.

The influence of temperature on the rate of enthalpy relaxation during isothermal aging was examined. Figure 8 shows an increase in the area of the anomalous endothermic peak of the glass during standing at various temperatures.

The area under the anomalous endothermic peak of the DSC curve of glass obtained at each aging point and 0 min are denoted by Q and Q_0, respectively.

Q/Q_0 was plotted against temperature at aging times from 0 to 60 min. At 336 and 351 K, the increase in the area under the anomalous endothermic peak of the DSC curve was slightly observed. At 346 K, the area under the anomalous endothermic peak increased gradually. At 341 K, the most remarkable increase was observed. In the case of indomethacin, stabilization by enthalpy relaxation during annealing occurred most remarkably at about 303 K.[3a] In the case of TMCD, it occurred most remarkably at 341 K.

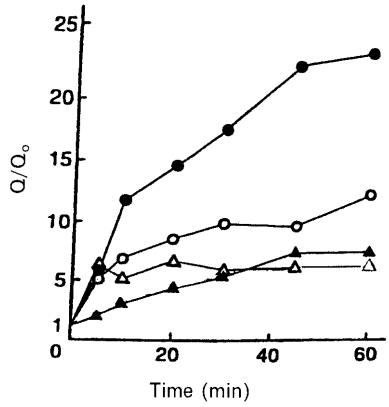

Fig. 8. Influence of Temperature on the Rate of Enthalpy Relaxation during Isothermal Aging below T_g

Temperature for isothermal aging: ▲, 336; ●, 341; ○, 346; △, 351 K.

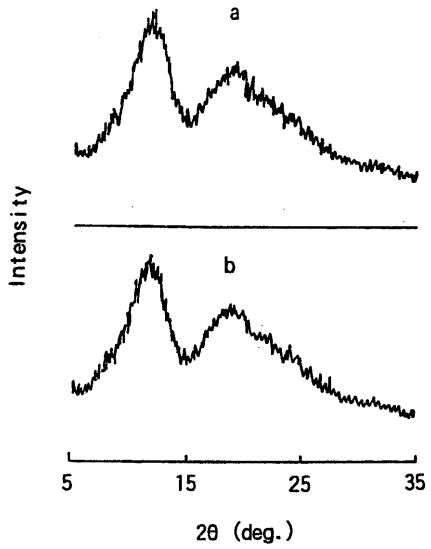

Fig. 9. X-Ray Diffraction Patterns of Pulverized Glassy TMCD

a, immediately after pulverization; b, 1 year.

For the presence of an optimum temperature at which the area under the anomalous endothermic peak is maximum, it seems that the mechanism is similar to that of indomethacin previously reported.[3a] At the aging time of 60 min, Q/Q_0 of TMCD (341 K) was 4 times larger than that of indomethacin (303 K). Enthalpy relaxation both during cooling and during the isothermal aging of glassy TMCD was larger than that of the pharmaceuticals previously reported.[3a,c] Such enthalpy relaxation may influence its physicochemical properties, because, for the crystallization of glassy indomethacin, Yoshioka *et al.*[9] reported that rapidly cooled sample(quenching) relaxes to an amorphous form more like the sample cooled slowly over the 36 h induction time.

6) Stability of Glassy TMCD after Pulverization In the previous paper, although glassy indomethacin was very stable, remaining as a glass for 2 years at room temperature, glassy phenobarbital with the same T_g as glassy indomethacin was unstable: devitrification occurred within a week. The crystallization of pulverized glassy indomethacin proceeded slowly.[3a] In the case of phenobarbital, it proceeded rapidly.[3b]

Glassy TMCD was stable, and devitrification did not occur for more than 1.5 years in a desiccator containing P_2O_5 at 25 °C. An attempt was made to elucidate the influence of pulverizing the glass on the transition to crystals by the X-ray method. Glassy TMCD was prepared by rapidly cooling the melt, and after pulverizing the glass in a mortar, 50—100 mesh fractions were collected by using sieves (JP XIII). The sample was stored in a desiccator containing P_2O_5 at 25 °C. Figure 9 shows the X-ray diffraction patterns of pulverized glassy TMCD. A halo was observed in the X-ray diffraction pattern of the sample immediately after pulverization.

Also, after one year, the halo could still be observed.

The pulverized glassy TMCD was in an amorphous state and remained as glass for one year. It was found that the glassy TMCD was extremely stable and TMCD was a good glass-former.

In conclusion, the thermal properties and stability of glassy TMCD were investigated by DSC and X-ray analysis, and it was found that TMCD has high glass-forming ability and glassy TMCD was extremely stable. This result for the stability of glassy TMCD may be due to the weak intermolecular interaction of TMCD.[2]

References and Notes

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