Glassy State of Pharmaceuticals. IV.[1] Studies on Glassy Pharmaceuticals by Thermomechanical Analysis[2]

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The glassy state of indomethacin was examined by thermomechanical analysis (TMA). The influences of the method of preparation and the measurement conditions of the sample on the TMA curves were investigated. The TMA curves of glassy indomethacin having hemispherical and plane surfaces were examined. Expansion was observed on the TMA curves in the region of glass transition temperature (T_g), which had been confirmed by differential scanning calorimetry. The TMA curves for the sample with the plane surface showed distinct expansion. It was further found that the glass transition shifted to lower temperatures as the heating rate was decreased and the loading increased. The TMA curves of brucine, griseofulvin and phenobarbital were similar to that of indomethacin. The relaxation process of glassy indomethacin below T_g was followed in terms of the variation of mechanical properties of samples.

Keywords glassy state; pharmaceutical; glass transition temperature; enthalpy relaxation; thermomechanical analysis; differential scanning calorimetry

In recent years, thermomechanical analysis (TMA) has been used to investigate thermal properties of polymers, glasses, ceramics, metals, *etc.*[3] In the pharmaceutical field, a number of studies using TMA have been reported for the determination of the glass transition temperature (T_g), softening temperature and melting temperature (T_m) of polymer film coatings.[4]

In the present study, the preparation and TMA measurement of the stable glassy state of indomethacin[5] were examined. The TMA curves of glassy indomethacin with hemispherical and plane surfaces were determined. Also, the influences of heating rate and loading on the glass transition were investigated. In the previous study,[5] the relaxation process below T_g was followed in terms of the area under the anomalous endothermic peak of the differential scanning calorimetry (DSC) curves and it was revealed that stabilization by enthalpy relaxation occurred during standing. In comparison with this enthalpy relaxation, the variation of mechanical properties of glassy pharmaceuticals with the passage of time was studied by TMA.

Experimental

Materials Brucine, griseofulvin, indomethacin and phenobarbital were of reagent grade.

Preparation of Samples The samples used for the TMA studies were prepared as follows. Crystalline powders were piled in a heap or placed flat in an aluminum sample pan for DSC and melted by heating with a mantle heater. The melts were solidified by allowing them to cool to room temperature on standing and the glass with a hemispherical or plane surface was obtained. In other cases, preparation of glass was done in the same way as reported in the previous paper.[5]

DSC A Perkin Elmer DSC-2 differential scanning calorimeter was used. Measurement conditions were the same as those reported in the previous paper.[5]

TMA A Perkin Elmer TMS-2 thermomechanical analysis system was used. The penetration probe used for the measurement was a flat-ended rod, 0.8 mm in diameter. The sample was placed on the platform of the fixed quartz sample tube. Both the sample and probe tip were heated or cooled by the surrounding furnace or coolant. Ice was used as the coolant. Measurements were made with loading ranging from 4 to 50 g. The heating procedures were always carried out under a nitrogen purge.

Results and Discussion

Since glassy indomethacin is extremely stable,[5] indomethacin was chosen as the material for TMA studies. The influences of the method of preparation of the sample and the measurement conditions on TMA curves were investigated.

Glass is more difficult to handle than polymer film, fiber, *etc.*, because glass is brittle and is liable to adhere to the sample tube and probe. Thus, the glass was prepared in an aluminum sample pan for DSC and a thin cover of aluminum (sample pan cover for Perkin Elmer DSC) was placed on the top of the sample to prevent adhesion. Use of the pan and the aluminum cover had been confirmed not to influence the TMA curves in the temperature region of measurement.

(1) Influence of Shape of Sample on Glass Transition To examine the influence of shape on the glass transition,

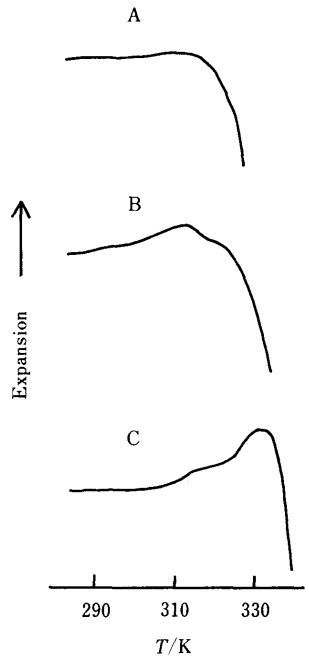

Fig. 1. Typical TMA Curves of Glassy Indomethacin with Surfaces of Different Shape

A: type (A); sample with hemispherical surface; thickness, 400 μm; diameter, 4 mm. B: type (B); sample with plane surface; thickness, 150 μm; diameter, 4 mm. C: type (C); sample with plane surface; thickness, 400 μm; diameter, 7 mm. Heating rate, 5 K/min; load, 5 g; range, 100 μm.

glassy indomethacin with surfaces of different shape were used. Figure 1 shows typical TMA curves.

In all cases, expansion on the TMA curves was observed in the region of T_g (321 K), which had been confirmed by DSC. The TMA curves for samples of type(B) and type(C) showed distinct expansion curves. Above the region of T_g, the TMA curves showed abrupt shrinkage with increase of temperature because of the deformation or spreading of the sample as the viscosity decreased.

In view of the consistency between T_g of DSC and the TMA results and the reproducibility of the TMA curve, experiments were carried out using the samples of type(A) and type(B).

(2) Influence of Heating Rate on Glass Transition The influence of heating rate on the glass transition of indomethacin samples of type(A) and type(B) was examined. The results for the load of 20 g are shown in Fig. 2. In the case of the sample of type(B), slight expansion was observed in the region of the T_g. In the case of the sample of type(A), the expansion was not observed. The glass transition of both samples shifted to lower temperatures as the heating rate was decreased. From the standpoint of thermal conductivity of the sample, moderate heating rates such as 2.5, 5, and 10 K/min are recommended in general. Also, for comparison with the DSC results,[5] TMA experiments were carried out at a rate of 5 K/min, which had been used in DSC studies.

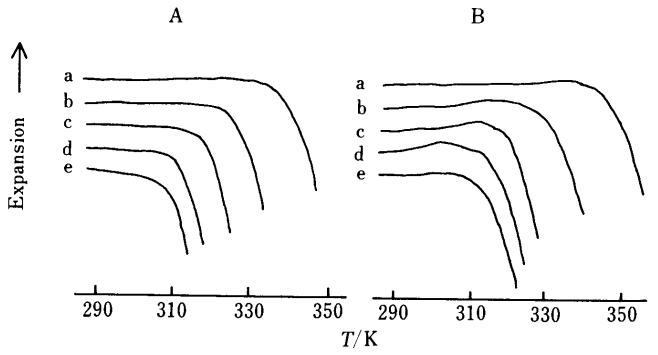

Fig. 2. Influence of Heating Rate on the TMA Curves for Indomethacin Samples of Type (A) and Type (B)

A, type (A); B, type (B). Heating rate: a, 20; b, 10; c, 5; d, 2.5; e, 1.25 K/min. Load, 20 g; range, 50 μm.

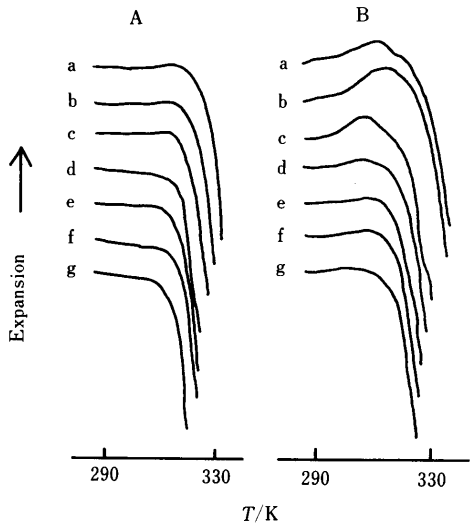

Fig. 3. TMA Curves of Glassy Indomethacin under Various Loadings

A, type (A); B, type (B). Load: a, 4; b, 5; c, 10; d, 20; e, 30; f, 40; g, 50 g. Heating rate, 5 K/min; range, 50 μm.

(3) Influence of Loading on Glass Transition The influence of loading on the glass transition of indomethacin samples of type(A) and type(B) was examined. Measurements were made at loadings from 4 to 50 g. The results are shown in Fig. 3.

For the sample of type(A), expansion was not observed. In the case of the sample of type(B), expansion was clearly observed when measurement was carried out with light loading (4, 5, and 10 g). The glass transition of both samples shifted to lower temperatures as the loading was increased.

For the comparison of some glassy pharmaceuticals with glassy indomethacin, the influence of loading on T_g was examined. Phenobarbital[1] was used as a sample with the same T_g as indomethacin. Also, brucine and griseofulvin were examined as samples with comparatively high T_g values of 365 and 370 K, respectively.[6]

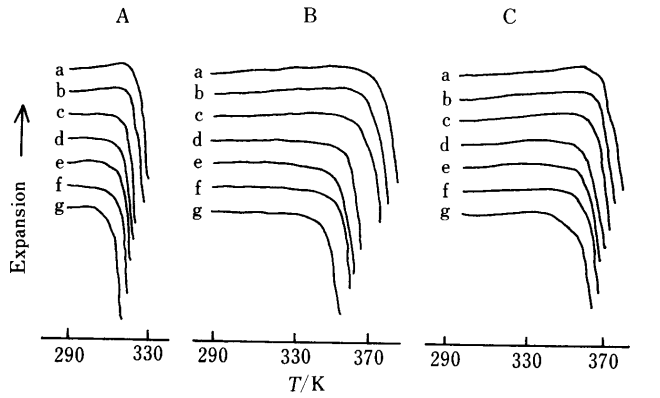

Fig. 4. TMA Curves of Glassy Phenobarbital, Brucine and Griseofulvin under Various Loadings

A, phenobarbital; B, brucine; C, griseofulvin. Load: a, 4; b, 5; c, 10; d, 20; e, 30; f, 40; g, 50 g. Heating rate, 5 K/min; range, 50 μm.

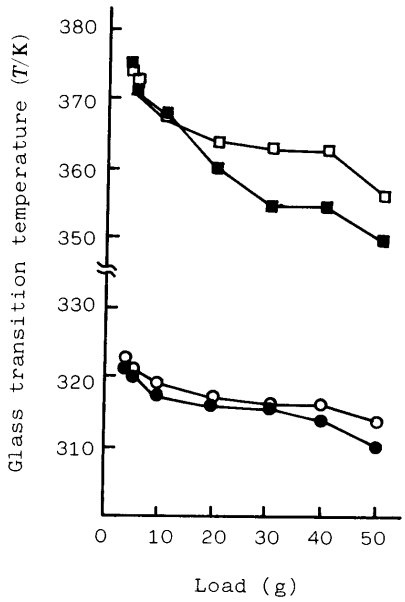

Fig. 5. Influence of Loading on T_g of Indomethacin, Phenobarbital, Brucine and Griseofulvin

○, indomethacin; ●, phenobarbital; □, griseofulvin; ■, brucine. Heating rate, 5 K/min.

The results for the sample of type(A) are shown in Fig. 4. The TMA curves of phenobarbital, brucine and griseofulvin were similar to that of indomethacin.

The T_g has been widely determined as the crossing point of the extrapolated lines from the two linear portions of the TMA curve, and so this method was employed in the present investigation. Figure 5 shows the variation of T_g with loading for the four pharmaceuticals.

The T_g decreased as the loading increased, but in the region of intermediate loading, T_g remained constant or decreased gradually, while at loadings over 40 g, T_g decreased rapidly again.

(4) Enthalpy Relaxation and TMA In the previous paper,[5] the relaxation process below T_g of glassy indomethacin was followed in terms of the area under the anomalous endothermic peak of the DSC curves and it was found that stabilization by enthalpy relaxation occurred during standing.

In the present paper, the variation of mechanical properties of glassy pharmaceuticals by enthalpy relaxation was studied by TMA. Figure 6A shows effect of relaxation at room temperature on DSC curves of glassy indomethacin.

The area under the anomalous endothermic peak of the DSC curve increased with aging time, showing that the enthalpy relaxation proceeded gradually during standing at room temperature. The TMA results are shown in Fig. 6B. In order to detect the expansion clearly, samples of type(B) was used with the load of 4 g. The TMA curve for the sample immediately after preparation showed gradual expansion in the neighborhood of room temperature and the expansion reached a peak at about 315 K. Then, it showed a smooth curve toward shrinkage. A shoulder was seen at 318 K. The expansion curve became sharper with a more distinct shoulder portion with aging, but after 15 d the shoulder disappeared and shrinkage occurred rapidly. Below T_g, the expansion curve became sharper with increasing aging time. In the case of the TMA method, the effect of relaxation is shown by the change of shape of the TMA curves.

The relaxation process of glassy brucine was followed in terms of TMA. In order to detect the expansion clearly, a sample of type(B) was used with the load of 4 g. Figure 7 shows the effect of relaxation at room temperature on TMA curves of brucine from below T_g to above T_m.

The TMA curve for the sample immediately after preparation showed gradual expansion up to the glass transition region which had been confirmed by the DSC. Above the region of T_g, the TMA curve showed gradual shrinkage because of the increase of fluidity of the sample up to T_m (450 K). The TMA curves in the range from below T_g to the glass transition region at about 380 K varied gradually with aging time. On the other hand, above 380 K, TMA curves showed different and unreproducible shapes, because the sample is in the supercooled liquid state, *i.e.* in a metastable state.

The TMA curves of brucine near T_g were obtained with higher sensitivity settings. The DSC and TMA curves of brucine near T_g are compared in Fig. 8.

In the case of indomethacin, the anomalous endothermic

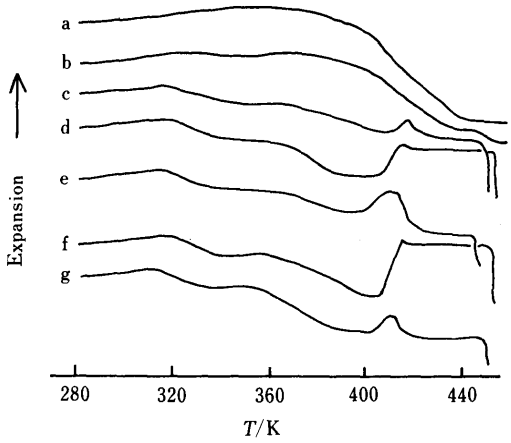

Fig. 7. Effect of Relaxation at Room Temperature on TMA Curves of Brucine from below T_g to above T_m

Load, 4 g; heating rate, 5 K/min; range, 500 μm. a, immediately after preparation; b, 1 d; c, 5 d; d, 7 d; e, 9 d; f, 14 d; g, 30 d.

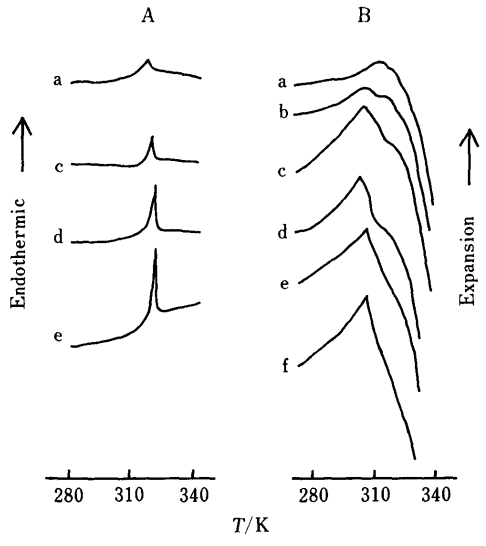

Fig. 6. Effect of Relaxation at Room Temperature on DSC and TMA Curves of Glassy Indomethacin

A: DSC curves; heating rate, 5 K/min. B: TMA curves; heating rate, 5 K/min; load, 4 g; range, 50 μm. a, immediately after preparation; b, 1 d; c, 2 d; d, 5 d; e, 15 d; f, 22 d.

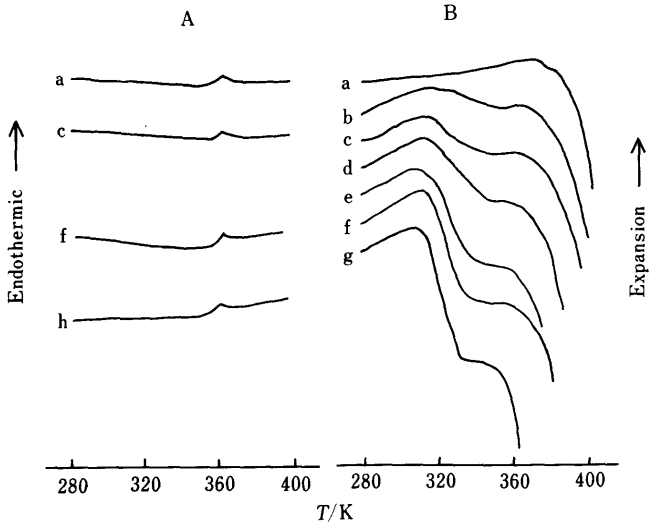

Fig. 8. Comparison of DSC and TMA Curves of Brucine Near T_g

A: DSC curves; heating rate, 5 K/min. B: TMA curves; heating rate, 5 K/min; load, 4 g; range, 50 μm. a, immediately after preparation; b, 1 d; c, 2 d; d, 3 d; e, 4 d; f, 5 d; g, 9 d; h, 12 d.

peak increased with aging time as shown in Fig. 6A. In the case of brucine, the increase of the anomalous endothermic peak was scarcely observed, as shown in Fig. 8A. These results indicate that the relaxation rate of glassy brucine at room temperature was extremely slow, presumably because of the comparatively high T_g value.

The TMA curve for glassy brucine immediately after preparation showed gradual expansion up to 380 K. After 1 d of aging, the sample showed expansion to 320 K and then shrinkage was observed. In the case of glassy indomethacin, below T_g, expansion curve became sharper with increasing aging time as shown in Fig. 6B. Although the expansion curve of brucine did not vary with aging time, the shrinkage accompanied by a shoulder was more clearly observed with aging time. It appears that the mechanical behavior of glassy brucine reflects the relaxation at room temperature, and TMA could be used to detect the glassy state of brucine.

References and Notes

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