Glassy State of Pharmaceuticals. III.[1] Thermal Properties and Stability of Glassy Pharmaceuticals and Their Binary Glass Systems[2]

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Glassy pharmaceuticals were prepared by cooling the melts and their state was confirmed by measuring the glass transition temperature (T_g) and the anomalous endothermic peak (heat capacity maximum) in the differential scanning calorimetry (DSC) curves. Glass formation was found for 20 pharmaceuticals (aspirin, phenobarbital, antipyrine and so on). The values of the ratio of T_g and melting temperature (T_m) of these pharmaceuticals lay between 0.59 and 0.84. Although the 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, and devitrification occurred within a week. Thus the rate of crystallization of pulverized glassy phenobarbital was determined by the X-ray diffraction method. The crystallization of pulverized glassy phenobarbital proceeded rapidly and the degree of crystallinity reached a maximum of 75% after 24 h.

Crystallization of glassy salicin was followed by means of DSC curves. It was revealed that stabilization by enthalpy relaxation occurred simultaneously with the crystallization in glassy salicin during standing.

Binary glass systems of pharmaceuticals were prepared with the aim of improving the stability of the glass, and several thermal properties of binary glass systems were investigated.

Keywords glassy state; pharmaceutical; glass transition temperature; stability; crystallization; enthalpy relaxation; differential scanning calorimetry; X-ray analysis

In the previous papers,[1] the existence of the glassy state of indomethacin was confirmed by detection of the jump of heat capacity and the anomalous endothermic peak in the differential scanning calorimetry (DSC) curves. Several thermal properties of glassy indomethacin, that is, the effects of cooling rate of the melt and the heating rate of the glass on the glass transition, the apparent activation energy of the glass transition and the relaxation process below the glass transition temperature (T_g) were investigated by analysis of DSC curves. Some pharmaceutical properties of the glassy indomethacin were also studied and it was revealed that the glass dissolved faster and was absorbed more than crystalline indomethacin in rabbits.

In the present paper, some glassy pharmaceuticals were prepared by cooling the melts and the existence of the glassy state was confirmed by detection of T_g and the anomalous endothermic peak in DSC curves. The relationship between T_g and melting temperature (T_m) was investigated. Crystallization of pulverized glassy phenobarbital was investigated by the X-ray diffraction method and the result was compared with that reported for pulverized glassy indomethacin by the authors.[1] It was revealed by DSC measurements that stabilization by enthalpy relaxation occurred simultaneously with the crystallization in glassy salicin during standing.

Moreover, in an attempt to improve the stability of the glassy pharmaceuticals, binary glass systems were prepared and their thermal properties were investigated.

Experimental

Materials Sulfisoxazole, sulfathiazole, sulfadimethoxine, aspirin, phenobarbital, antipyrine, phenylbutazone, quinine ethylcarbonate, tartaric acid and santonin were of JP grade and other materials were of reagent grade.

Preparation of Glass The preparation of glass was done in the same way as reported in the previous paper.[1]

DSC DSC curves were measured with DSC-2 (Perkin-Elmer) equipped with an Intracooler I system. Measurement conditions were the same as those reported in the previous paper.[1]

X-Ray Diffraction X-Ray diffraction patterns were measured as reported in the previous paper.[1]

Thin-Layer Chromatography (TLC) The chemical stability of pharmaceuticals during treatment of the sample was checked by using TLC. The samples dissolved in acetone were spotted on silica gel plates, which were developed with appropriate solvent systems. The spots were detected under ultraviolet light.

Results and Discussion

1) Glass Transition Temperature of Glassy Pharmaceuticals Table I shows the T_g, T_m and the T_g/T_m values of the pharmaceuticals forming glasses above room tempera-

TABLE I. Pharmaceuticals Forming Glasses above Room Temperature

Pharmaceutical	T_g (K)	T_m (K)	T_g/T_m
Cholecalciferol	296	352	0.84
Sulfisoxazole	306	460	0.67
Stilbestrol	308	439	0.70
Phenobarbital	321	443	0.72
Quinidine	326	445	0.73
Salicin	333	466	0.71
Sulfathiazole	334	471	0.71
Sulfadimethoxine	339	465	0.73
Dehydrocholic acid	348	502	0.69
17β-Estradiol	354	445	0.80

TABLE II. Pharmaceuticals Forming Glasses below Room Temperature

Pharmaceutical	T_g (K)	T_m (K)	T_g/T_m
Aspirin	243	408	0.59
Antipyrine	256	380	0.67
Methyltestosterone	270	421	0.64
Phenylbutazone	277	377	0.73
Quinine ethylcarbonate	278	362	0.77
Progesterone	279	399	0.70
Atropine	281	379	0.74
Tartaric acid	289	430	0.67
Santonin	290	434	0.67
Ergocalciferol	290	376	0.77

ture. Glassy dehydrocholic acid and 17β-estradiol had relatively high T_g values and T_g of glassy phenobarbital was the same as that of glassy indomethacin reported in the previous paper.[1] These glassy pharmaceuticals remained stable for at least 2 months except stilbestrol, phenobarbital and salicin, which crystallized within a week.

Table II shows the T_g, T_m and the T_g/T_m of the pharmaceuticals forming glasses below room temperature. These pharmaceuticals existed as supercooled liquids at room temperature. The T_g values of glassy aspirin and antipyrine were the lowest in this group.

Decomposition during treatment of the sample was observed by TLC for cholecalciferol, quinidine, sulfadimethoxine, progesterone and ergocalciferol.

2) Relationship between T_g and T_m Values of T_g/T_m of pharmaceuticals have scarcely been reported so far. However, it is known that T_g/T_m is about 0.5 for many symmetrical polymers such as polyethylene and 0.7 for many asymmetrical polymers such as polyisoprene.[3]

As shown in Tables I and II, the T_g/T_m values of glassy pharmaceuticals lay between 0.59 and 0.84 and were slightly larger than those of polymers. Figure 1 shows the relationship between T_g and T_m of glassy pharmaceuticals. The oblique lines originate from the absolute zero point and the slopes of the lines give the T_g/T_m. The T_g/T_m values of most pharmaceuticals were distributed in the range of 0.67 to 0.8 and that of 0.59 for aspirin was the smallest among the samples examined in the present study.

3) Crystallization of Glassy Phenobarbital In order to elucidate the relation between T_g and the stability of the glassy pharmaceuticals, crystallization of glassy indomethacin and phenobarbital with the same T_g of 321 K was investigated. Although the devitrification of glassy indomethacin did not occur for at least 2 years at room temperature,[1] intact glassy phenobarbital crystallized within a week. Then, the crystallization of pulverized glassy phenobarbital was investigated by the X-ray diffraction method and compared with that of pulverized glassy indomethacin reported previously.[1]

A mass of glassy phenobarbital was pulverized in a mortar and the 50—100 mesh fraction was collected by using sieves (JP XI) and stored in desiccator containing silica gel at room temperature. Figure 2 shows the X-ray diffraction patterns of pulverized glassy phenobarbital at various storage times. The scattering intensity of crystalline phenobarbital increased with the lapse of time up to 24 h.

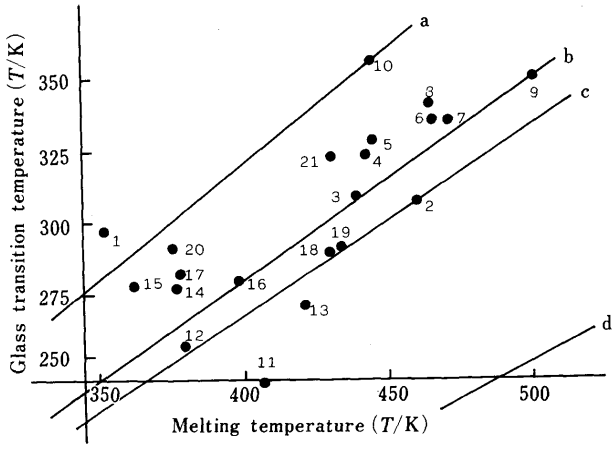

Fig. 1. Relationship between T_g and T_m of Various Pharmaceuticals

The oblique lines originate from the absolute zero point and the slopes give T_g/T_m. a, 0.80; b, 0.70; c, 0.67; d, 0.50. 1, cholecalciferol; 2, sulfisoxazole; 3, stilbestrol; 4, phenobarbital; 5, quinidine; 6, salicin; 7, sulfathiazole; 8, sulfadimethoxine; 9, dehydrocholic acid; 10, 17β-estradiol; 11, aspirin; 12, antipyrine; 13, methyltestosterone; 14, phenylbutazone; 15, quinine ethylcarbonate; 16, progesterone; 17, atropine; 18, tartaric acid; 19, santonin; 20, ergocalciferol; 21, indomethacin.

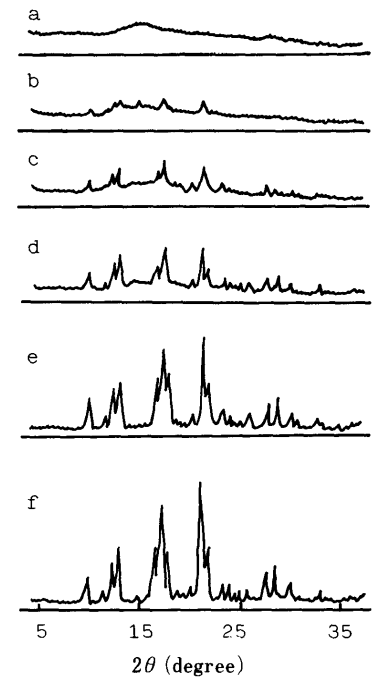

Fig. 2. The Variation of X-Ray Diffraction Patterns of Pulverized Glassy Phenobarbital with Time

a, immediately after pulverization; b, 2 h; c, 3 h; d, 4 h; e, 7 h; f, 24 h.

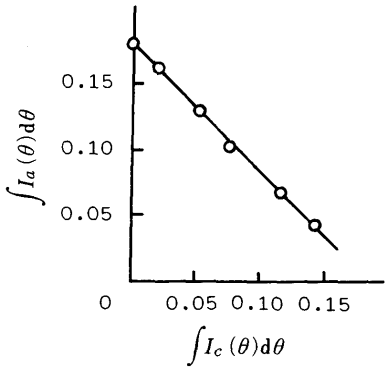

Fig. 3. The Regression Line for the Scattering Intensities from Crystalline and Amorphous Regions of Phenobarbital, Samples with Different Crystallinities Obtained by Hermans' Method

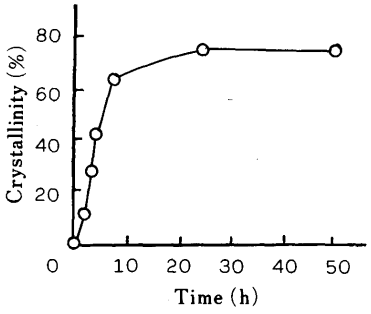

Fig. 4. The Rate of Crystallization of Pulverized Glassy Phenobarbital

$\int I_c(\theta)d\theta$ was plotted against $\int I_a(\theta)d\theta$ as shown in Fig. 3, where $\int I_c(\theta)d\theta$ and $\int I_a(\theta)d\theta$ are the integrated intensities of scattering from crystalline and amorphous regions, respectively. There is a linear relationship between $\int I_c(\theta)d\theta$ and $\int I_a(\theta)d\theta$. The slope was calculated to be -1.02 by the least-squares method, and the crystallinity of phenobarbital was calculated by Hermans' method.[1,4] The results are shown in Fig. 4 as a function of time.

After an induction period, glassy phenobarbital crystallized rapidly. It took 24 h to reach maximum crystallization, and at this stage phenobarbital has 75% crystallinity. Thus, glassy phenobarbital was extremely unstable compared with indomethacin, although the T_g values were the same and the T_g/T_m values were nearly the same for both pharmaceuticals.

These findings might be interpreted in terms of steric structure, symmetry and hydrogen bonding of the molecules in the glasses.

4) Stabilization by Enthalpy Relaxation and Crystallization of Glassy Salicin In the previous paper,[1] the isothermal enthalpy relaxation process of glassy indomethacin below T_g was traced in terms of the area under the anomalous endothermic peak in the DSC curve. It was revealed the main factors influencing the relaxation process are aging time and temperature, and the rate of relaxation during annealing was found to reach the maximum at about 303 K. In the present study, stabilization by enthalpy relaxation and crystallization of glassy salicin with the comparatively high T_g of 333 K during standing were followed by means of DSC curves. The crystallinity of glassy salicin could not be determined by Hermans' X-ray diffraction method because the ratios of the intensities of individual peaks to the total intensity of crystalline peaks were not constant.

Glassy salicin was prepared by cooling the melt rapidly, and after pulverizing the glass, the sample was stored in a desiccator containing silica gel at room temperature. The change of enthalpy during standing was followed by DSC measurements. Figure 5 shows the DSC curves of pulverized glassy salicin at various storage times. While no peak was observed above the glass transition in the DSC curve of the intact glass (Fig. 5a), the exothermic peak for crystallization of the glass was observed in the DSC curves for the pulverized glass (Fig. 5b—i). This exothermic peak is interpreted in terms of the crystallization of a portion of the glass during heating above T_g.

The exothermic peak decreased gradually with lapse of time. Further, the jump of heat capacity and the anomalous endothermic peak for the glass transition increased gradually up to 5 d and then decreased. The increase in the anomalous endothermic peak indicates enthalpy relaxation of the glass during standing. These results show that stabilization by enthalpy relaxation and crystallization took place at the same time in glassy salicin.

The jump of heat capacity, the anomalous endothermic peak and the exothermic peak for crystallization disappeared gradually. Finally, only the endothermic peak for fusion of the crystals at the melting point was observed in the DSC curve (Fig. 5j). This result indicates that the crystallization was completed at this stage.

5) Binary Glass System of Pharmaceuticals In an attempt to improve the stability of the glasses, the preparation of binary glass systems was attempted and their variation of T_g with the ratio of the components were investigated. Figure 6 shows the variation of T_g of the salicin (component 1)–phenobarbital (component 2) binary glass system with the component ratio. The T_g of the binary glass system varied linearly with weight fraction of salicin. The Gordon–Taylor equation[5] was applied for the evaluation of the randomness characteristics of the glass system.

The theory derived by Gordon and Taylor assumes that the T_g of the ideal copolymer is determined by the weight fraction, and indeed, T_g of the components is known to be applicable to many copolymer systems for the evaluation of the randomness characteristics. The relation is expressed by the following equation:

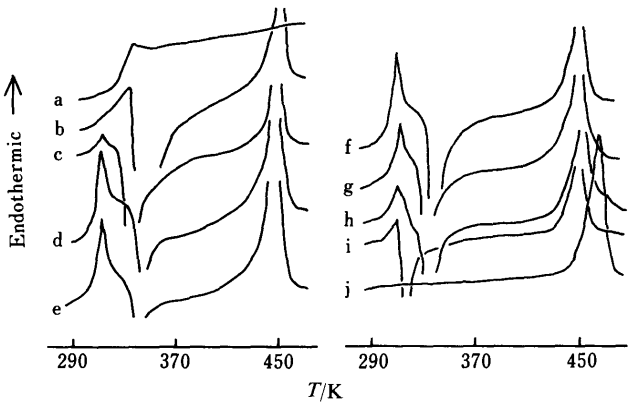

Fig. 5. Variation of DSC Curves of Glassy Salicin during Standing after Pulverization

a, intact glass; b, immediately after pulverization; c, 15 h; d, 2 d; e, 3 d; f, 5 d; g, 7 d; h, 8 d; i, 11 d; j, 12 d.

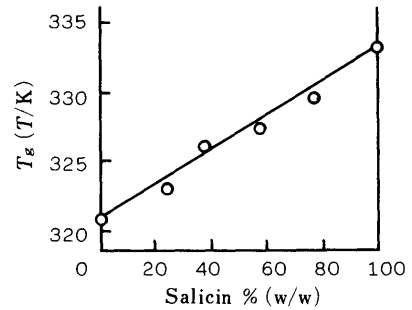

Fig. 6. Variation of T_g of the Phenobarbital–Salicin Binary System

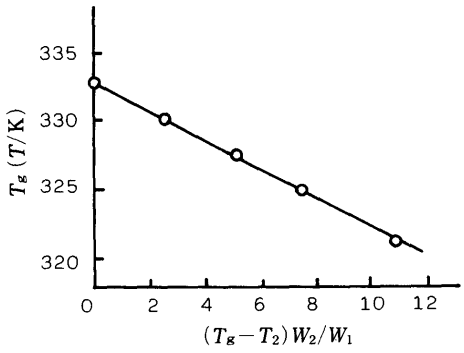

Fig. 7. Analysis of the Phenobarbital–Salicin Binary System in Terms of the Gordon and Taylor Equation

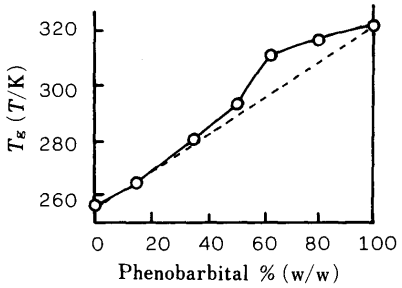

Fig. 8. Variation of T_g of the Antipyrine–Phenobarbital Binary System
----, theoretical relationship; ——, observed relationship.

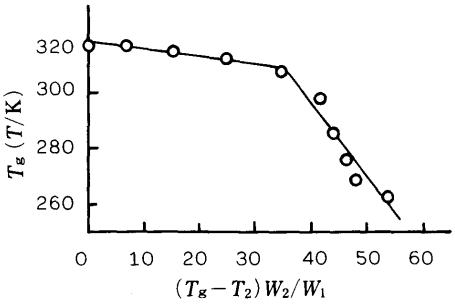

Fig. 9. Deviation of the Antipyrine–Phenobarbital Binary System from the Gordon and Taylor Equation

$$T_g = -k(T_g - T_2)W_2/W_1 + T_1 \quad (1)$$

where W_1 and W_2 are the weight fractions of components 1 and 2, T_1 and T_2 are the homopolymer T_g values of components 1 and 2, and k is a coefficient defined by $k = \Delta\beta_1/\Delta\beta_2$, where $\Delta\beta$ expresses the difference of expansion coefficients below and above T_g.

The data for the glass system in Fig. 6 were plotted according to the Gordon–Taylor equation, as shown in Fig. 7. There is a linear relationship between weigt ratio of salicin and T_g. The system thus obeys the ideal situation described by Eq. 1. This result indicate that salicin and phenobarbital were mixed randomly in the binary glass system without any interaction.

The results for the binary glass system of phenobarbital (component 1) and antipyrine (component 2) are shown in Figs. 8 and 9. As shown in Fig. 8, when the content of phenobarbital in the glass system was larger than 20%, T_g of the binary glass system was above the straight line connecting the T_g of each component, and the deviation from the line was found to be maximum at 60%. When the data for this system were plotted according to the Gordon–Taylor equation (Fig. 9), two straight lines were obtained intersecting in the vicinity of 60% phenobarbital content.

The result for the indomethacin (component 1) and antipyrine (component 2) binary glass system is shown in Figs. 10 and 11. As shown in Fig. 10, T_g of the binary glass

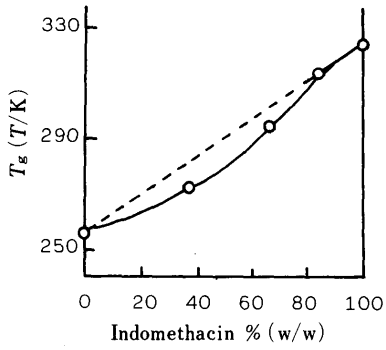

Fig. 10. Variation of T_g of the Antipyrine–Indomethacin Binary System
----, theoretical relationship; ——, observed relationship.

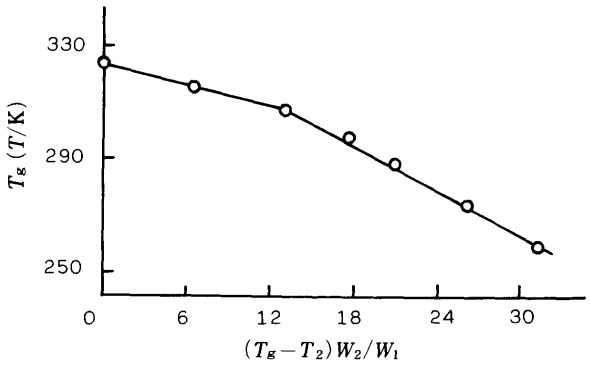

Fig. 11. Deviation of the Antipyrine–Indomethacin Binary System from the Gordon and Taylor Equation

system was below the line connecting the T_g of each component. When the data for the glass system were plotted according to the Gordon–Taylor equation (Fig. 11), two straight lines having slightly different slope were obtained, and the deviation of this system from the Gordon–Taylor equation was relatively small.

The Gordon–Taylor plots of these binary glass systems indicate that the randomness characteristics of binary glass system varied, depending upon the components.

References and Notes

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