Physicochemical Stability of Glassy 16-Membered Macrolide Compounds

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Amorphous 16-membered macrolide compounds were prepared by spray drying, and the physicochemical stability of the amorphous states has been investigated. Josamycin, rokitamycin, midecamycin, 3-*O*-acetyl-4″-*O*-isovaleryltylosin, miocamycin and 4″-*O*-(4-methoxyphenyl)acetyltylosin were used as macrolide compounds. From X-ray powder diffractometry and differential scanning calorimetric (DSC) measurements, all the spray dried compounds were recognized to be in a glassy state. Miocamycin and 4″-*O*-(4-methoxyphenyl)acetyltylosin glasses showed crystallization and fusion peaks on DSC thermograms, and were crystallized after 6 months of storage at 313 K and 75% relative humidity. Other compounds showed only a glass transition peak on each DSC thermogram, and the glassy state was maintained stably against humidity. It was found that the physicochemical stability of the glassy state of miocamycin was closely related to the inlet temperature of the spray drying process.

Keywords amorphous; macrolide compound; spray drying; stability; glass; glass transition temperature

When a poorly water-soluble drug was orally administered, the rate of absorption and/or the extent of the amount absorbed was usually related to the dissolution rate of the drug in the gastrointestinal tract.[1-3] Various trials have been undertaken to increase the dissolution rate of poorly water-soluble drugs: pulverization, grinding with additives, inclusion compound formation, solid dispersion and the utilization of polymorphs.[4-10] Among these trials, the improvement of drug solubility using an amorphous form has become of interest in preparing solid dosage forms, even though the amorphous state is sometimes unstable for practical use.[11,12] There have been a number of reports about the stability of the amorphous state of various drugs.[13,14] Most of them, however, concerned amorphous drugs in solid dispersions with some additives; there are only a few reports regarding the physicochemical stability of amorphous drugs themselves.[15-17] In our previous report, we discussed the physicochemical stability of the glassy state of a new 16-membered macrolide compound, 4″-*O*-(4-methoxyphenyl)acetyltylosin, obtained by the spray drying of dichloromethane solution.[18] Different kinds of glassy states were prepared by controlling the inlet temperature of the spray dryer, and it was found that the inlet temperature between glass transition temperature (T_g) and crystallization temperature (T_c) was appropriate for preparing a stable glassy state. In the present paper, the glassy states of 6 macrolide compounds were prepared by spray drying and the thermal behavior of the glassy states was investigated using differential scanning calorimetry (DSC). The relationship between the stability of glassy state and its thermal properties was discussed.

Experimental

Materials 4″-*O*-(4-Methoxyphenyl)acetyltylosin (MAT), 3-*O*-acetyl-4″-*O*-isovaleryltylosin (AIV) and josamycin (JM) were produced in the central research laboratories of the Mercian Corporation. Midecamycin (MDM) was purchased from Wako Pure Chemical Industries, Ltd. Rokitamycin (RKM) and miocamycin (MOM) were isolated and purified from commercial tablets.

Preparation of the Glassy States of Drugs Glassy MAT, AIV, MDM and MOM were obtained by spray drying dichloromethane solutions of each compound using a spray dryer (Model SD-1, Tokyo Rikakikai Co., Ltd.). The concentration of the drugs was 100 mg/ml and the inlet temperature of the spray dryer was fixed at 363 K. In the case of MOM, several kinds of spray dried powders were prepared by varying the inlet temperatures to 363, 393 and 433 K. JM and RKM were originally obtained in the glassy state.[19,20]

X-Ray Powder Diffractometry X-Ray Powder diffraction patterns were determined by an X-ray diffractometer (Model JDX-8030, Nihon Denshi Co., Ltd., Ni-filtered, CuK_α, 40 kV, 20 mA, $2\theta = 5.0°$—$40.0°$, scan speed: 2.4°/min).

Thermal Analysis DSC measurements were carried out under a semi-closed condition using differential scanning calorimetry (Model DSC-50, Shimadzu Co., Ltd.). The heating rate was 10 K/min and nitrogen gas flowed at a rate of 50 ml/min. The enthalpy of crystallization ($|\Delta H_c|$) of amorphous MOM was calculated from the area of the exothermic peak due to crystallization on DSC curves, and indium was used as a standard material (99.98%, Wako Pure Chemical Industries, Ltd.; mp 429.4 K, $|\Delta H_m|$ 28.45 J/g).

Results and Discussion

X-Ray Powder Diffractometry and DSC Patterns of Crystalline and Glassy 16-Membered Macrolide Compounds The structural formulae of 16-membered macrolide compounds used in this study are shown in Fig. 1. The X-ray powder diffraction patterns of the crystalline and amorphous states of all the compounds, including MAT as previously reported,[18] are shown in Fig. 2. For the crystalline samples, a number of diffraction peaks were recognized, while for the amorphous samples, only a halo was observed in the diffraction patterns. It was impossible to obtain the crystalline states of JM and RKM.[19,20] The DSC curves of the crystalline and amorphous states of each compound are shown in Figs. 3 and 4. The crystalline specimens of MDM, MOM and MAT showed only an endothermic peak attributable to the melting. AIV has polymorphic forms, and the DSC thermogram of the crystalline form of AIV showed two endothermic peaks at 427.9 K and 467.8 K due to the melting of two crystalline forms. That is, the metastable form of AIV had a melting point of 427.9 K and the stable form of AIV crystallized after the fusion of the metastable form showed a melting point of 467.8 K.

On the other hand, the amorphous states of all the compounds showed a jump in heat capacity in the DSC

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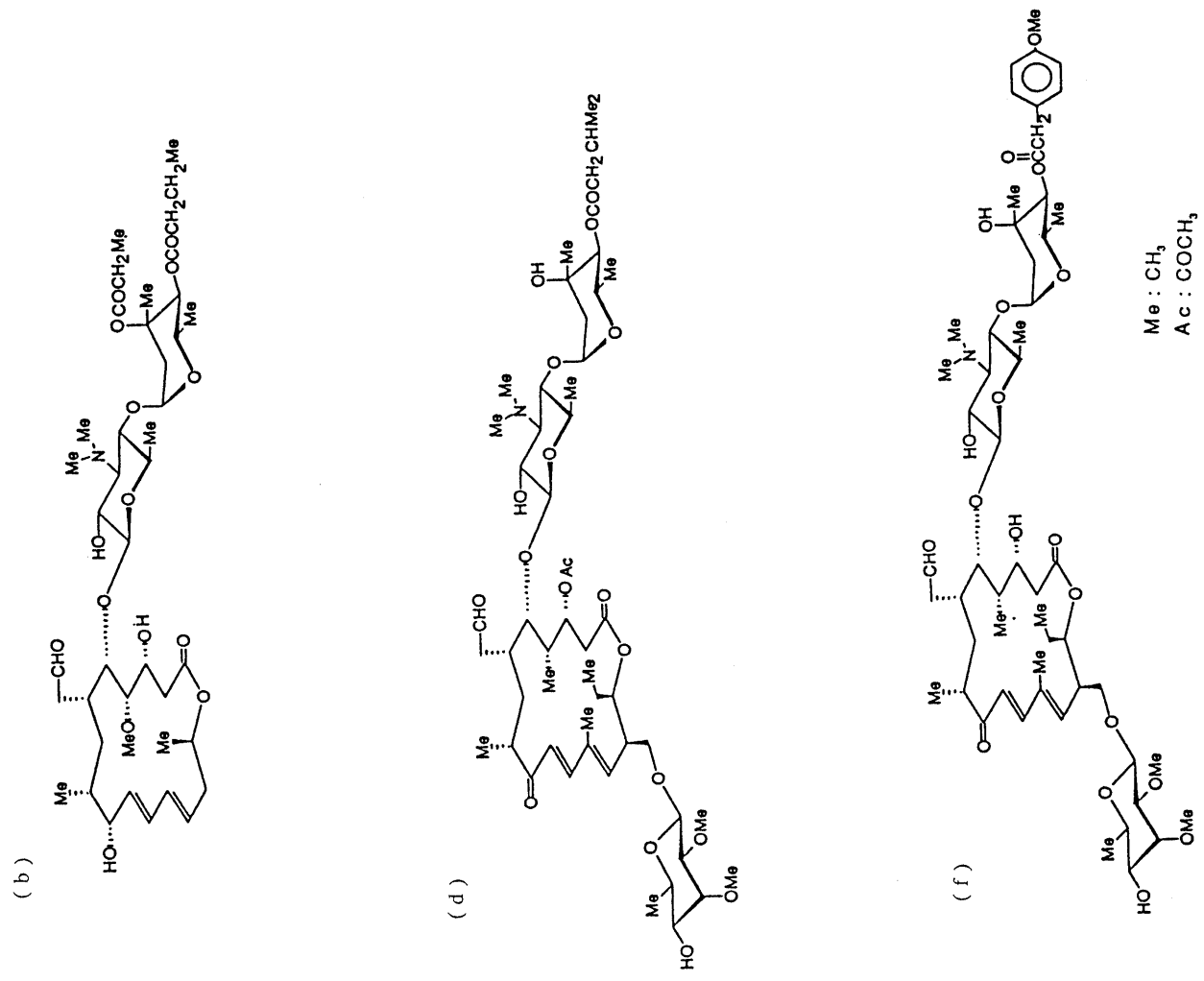

Fig. 1. Structures of 16-Membered Macrolide Compounds

(a) josamycin (JM), (b) rokitamycin (RKM), (c) midecamycin (MDM), (d) 3-*O*-acetyl-4″-*O*-isovaleryltylosin (AIV), (e) miocamycin (MOM), (f) 4″-*O*-(4-methoxyphenyl)acetyltylosin (MAT).

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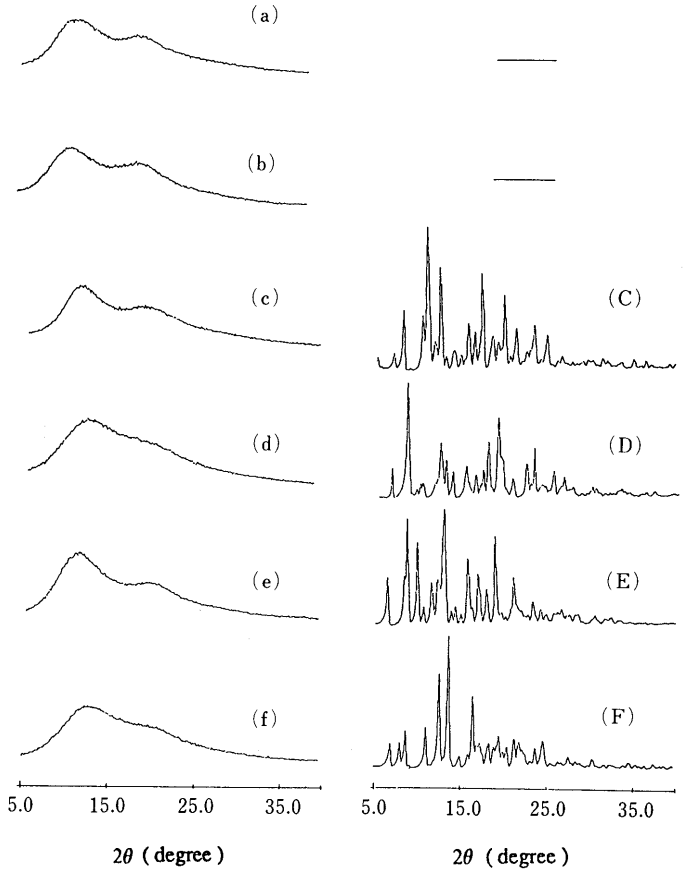

Fig. 2. X-Ray Powder Diffraction Patterns of Crystalline and Amorphous Macrolide Compounds

(a) josamycin (JM), (b) rokitamycin (RKM), (c), (C) midecamycin (MDM), (d), (D) 3-*O*-acetyl-4″-*O*-isovaleryltylosin (AIV), (e), (E) miocamycin (MOM), (f), (F) 4″-*O*-(4-methoxyphenyl)acetyltylosin (MAT).

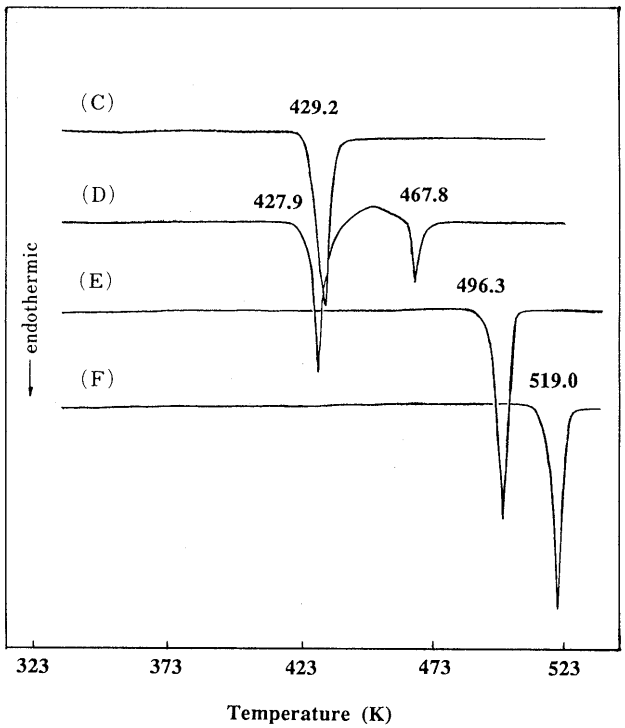

Fig. 3. DSC Curves of Crystalline Macrolide Compounds

(C) midecamycin (MDM), (D) 3-*O*-acetyl-4″-*O*-isovaleryltylosin (AIV), (E) miocamycin (MOM), (F) 4″-*O*-(4-methoxyphenyl)acetyltylosin (MAT).

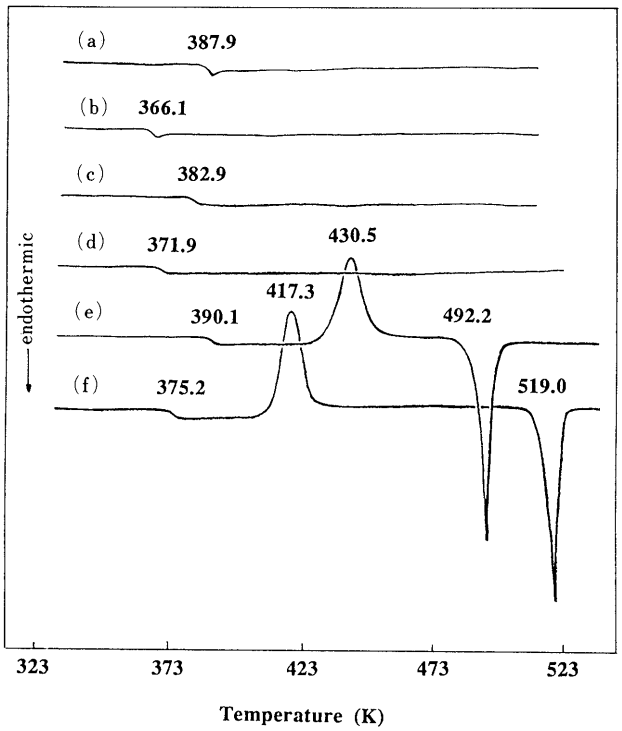

Fig. 4. DSC Curves of Amorphous Macrolide Compounds Prepared by Spray Drying

(a) josamycin (JM), (b) rokitamycin (RKM), (c) midecamycin (MDM), (d) 3-*O*-acetyl-4″-*O*-isovaleryltylosin (AIV), (e) miocamycin (MOM), (f) 4″-*O*-(4-methoxyphenyl)acetyltylosin (MAT).

TABLE I. Thermal Properties of Various 16-Membered Macrolide Compounds

Samples	Crystalline	Glassy			T_g/T_m
	T_m (K)	T_g (K)	T_c (K)	T_m (K)	
JM	—	387.9	—	—	—
RKM	—	366.1	—	—	—
MDM	429.2	382.9	—	—	0.89
AIV	α: 467.8, γ: 427.9	371.9	—	—	0.79[a], 0.87[a]
MOM	496.3	390.1	430.5	492.2	0.79
MAT	519.0	375.2	417.3	519.0	0.72

a) The values were obtained using the T_m of α- and γ-types of crystalline solids, respectively.

curves, as shown in Fig. 4, which characterized the glassy state. In the curves of amorphous MOM (e) and MAT (f), both an exothermic peak and an endothermic peak were observed after the jump in heat capacity. The X-ray powder diffraction patterns of MOM and MAT powders, which were removed from the DSC furnace immediately after the appearance of each exothermic peak, were identical to the patterns of each crystalline form, respectively. It was found that the jump in heat capacity, following exothermic and endothermic peaks on DSC curves, were attributed to the glass transition, the crystallization and the fusion, respectively, but the onset temperatures of MOM melting observed in Figs. 3 and 4 were a little different, presumably due to the different crystallite size of MOM. For the other drugs, the glassy state transformed to the super cooled liquid state at the glass transition temperature (T_g), and changed further into a fluid liquid continuously and concurrently with an increase in temperature. The results of the thermal

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behavior of the glassy macrolide compounds are compiled in Table I. The glassy states of all the substances exhibited a glass transition on DSC curves. For glassy MOM and MAT, an exothermic peak due to crystallization and an endothermic peak due to melting (T_m) were observed. The ratios of T_g to T_m were calculated to be between 0.72 and 0.89 for the macrolide compounds. Fukuoka *et al.* reported that the values of the ratio of T_g to T_m for a number of glassy pharmaceuticals were between 0.69 and 0.85.[16,17] Murthy *et al.* also reported the T_g/T_m values for organic liquids to be between 0.52 and 0.74.[21] The T_g/T_m value for MDM was slightly higher than that of many glassy materials.

Physicochemical Stability of a Glassy State The relationship between the physicochemical stability of a glassy state and the DSC patterns was investigated. The storage condition of the samples was fixed at 313 K and 75% RH; this condition is traditionally used to estimate the physicochemical stability of drug molecules for long-term storage.[22] Figure 5 shows the X-ray powder diffraction patterns of the glassy macrolide compounds after 6 months of storage at 313 K and 75% relative humidity (RH). The X-ray powder diffraction patterns of MOM and MAT showed sharp diffraction peaks, indicating the presence of crystalline compounds, although the peak intensities were not as high as those of intact crystals. On the other hand, no diffraction peaks due to crystals were observed in the X-ray diffraction patterns of the 4 other compounds. The glassy states of these compounds were hardly changed during 6 months of storage at 313 K and 75% RH.

It was noticed that the unstable glassy states of MOM and MAT showed exothermic peaks due to recrystallization and an endothermic peak due to melting on each DSC curve. By contrast, the stable glassy states of the 4 other compounds showed only T_g on the DSC curves.

In the previous paper, we reported that the physicochemical stability of the glassy state of MAT was affected by spray drying temperature. Matsuda *et al.* investigated the physicochemical stability of spray-dried furosemide by X-ray powder diffraction and thermal analysis, and concluded that the preparation of amorphous states which had varying stability against hygroscopicity was possible by varying the inlet temperature of the spray dryer.[15] As the DSC pattern of glassy MOM very closely resembles that of glassy MAT, as previously reported,[18] the effect of inlet temperature of the spray drying process on the stability of glassy MOM was studied. Glassy MOM samples were prepared by the spray drying of a dichloromethane solution of MOM, varying the inlet temperature of the spray dryer to 363, 393 and 433 K. Figure 6 shows the changes in X-ray powder diffraction patterns of MOM glassy states prepared using different inlet temperature conditions under storage at 313 K and 75% RH.

For the samples prepared at 363 K and 433 K (MSD-1 and MSD-3, respectively), the diffraction peaks due to MOM crystals were obvious after storage for 25 weeks. The diffraction peaks due to crystals, however, were barely detectable with glassy MOM prepared at 393 K (MSD-2), this temperature being between the T_g and T_c of glassy

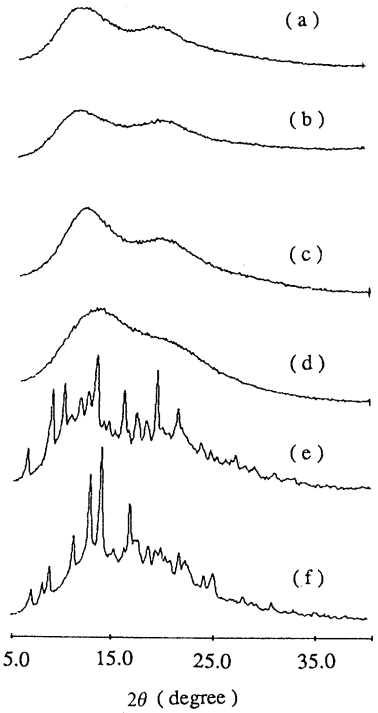

Fig. 5. X-Ray Powder Diffraction Patterns of Glassy Macrolide Compounds Prepared by Spray Drying after Storage for 6 Months at 313 K and 75% RH

(a) josamycin (JM), (b) rokitamycin (RKM), (c) midecamycin (MDM), (d) 3-*O*-acetyl-4″-*O*-isovaleryltylosin (AIV), (e) miocamycin (MOM), (f) 4″-*O*-(4-methoxyphenyl)acetyltylosin (MAT).

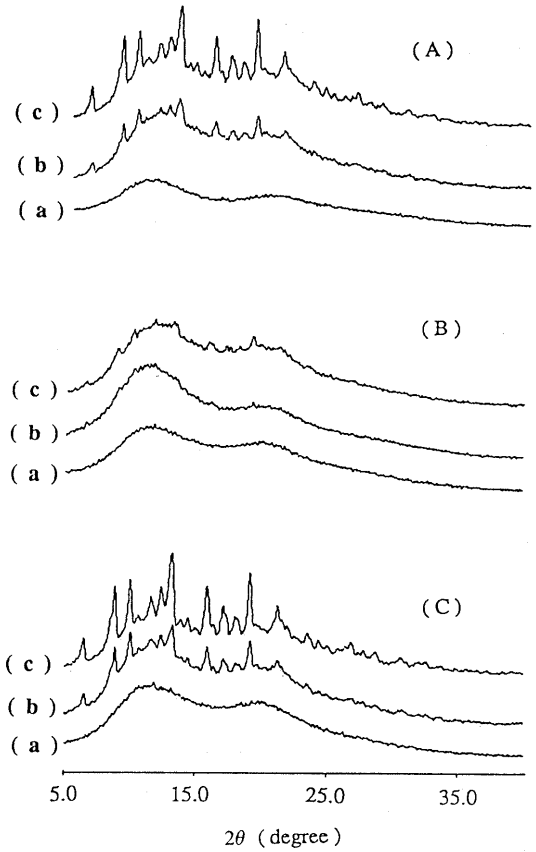

Fig. 6. Changes in X-Ray Powder Diffraction Patterns of Glassy Miocamycin (MOM) Prepared by Spray Drying at 313 K and 75% RH during Storage

(A) inlet temperature = 363 K, (a) initial, (b) 6 weeks, (c) 25 weeks. (B) inlet temperature = 393 K, (a) initial, (b) 6 weeks, (c) 25 weeks. (C) inlet temperature = 433 K, (a) initial, (b) 6 weeks, (c) 25 weeks.

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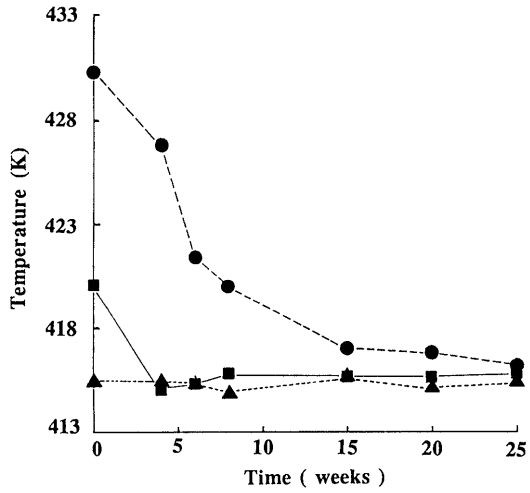

Fig. 7. Changes in T_c of Glassy MOM during Storage at 313 K and 75% RH

—■—, MSD-1 (inlet temperature = 363 K); ---●---, MSD-2 (inlet temperature = 393 K); ---▲---, MSD-3 (inlet temperature = 433 K).

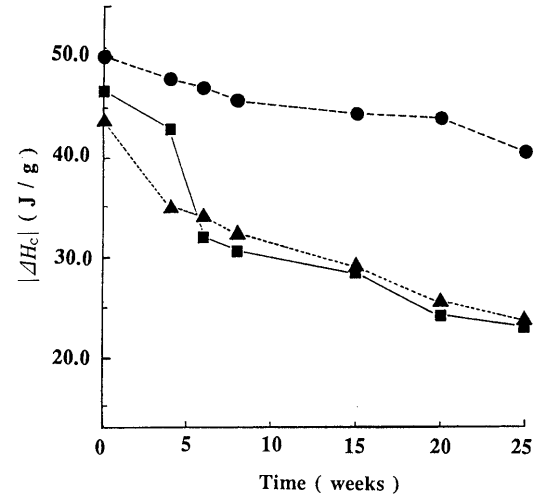

Fig. 8. Changes in Enthalpy of Crystallization of Glassy MOM during Storage at 313 K and 75% RH

—■—, MSD-1 (inlet temperature = 363 K); ---●---, MSD-2 (inlet temperature = 393 K); ---▲---, MSD-3 (inlet temperature = 433 K).

MOM. Figures 7 and 8 show the effect of storage at 313 K and 75% RH on the crystallization temperature (T_c) and the enthalpy of crystallization ($|\Delta H_c|$) of glassy MOM determined from DSC peak areas. Regarding T_c, great differences were observed at the initial stage of storage between MSD-2 and MSD-1 or 3, while the differences gradually became small during storage. A gradual decrease in $|\Delta H_c|$ was observed throughout the duration of storage in all of the systems. It was found, however, that the $|\Delta H_c|$ of MSD-2 was significantly greater than that of MSD-1 and -3, and that MSD-2 was more stable than MSD-1 and -3. These results of the stability experiments of glassy MOM were very similar to the results of glassy MAT reported in the previou paper.[18] In MSD-1 and -3 particles, some kind of micro-ordered structure of MOM molecules might occur during the drying process. On the other hand, in MSD-2, MOM was able to form a more stable glassy state which has a greater degree of disorder in the molecular arrangement. It was concluded that the most stable glassy state was obtained by controlling the inlet temperature to between T_g and T_c in the spray drying process.

In the present work, the amorphous states of all 16-membered macrolide compounds used in this work exhibited T_g on the DSC curves. The DSC patterns of the glassy states of macrolide compounds were classified into two groups as follows: (1) compounds which show only a jump of heat capacity (T_g), (2) compounds which show three thermal behaviors, glass transition, a subsequent exothermic peak due to crystallization, and an endothermic peak due to melting. As the results of storage experiments of the glassy states at 313 K and 75% RH, the recrystallization of group-1 glassy compounds was not observed, while glassy compounds belonging to group-2 (MOM and MAT) transformed into a crystalline state after 6 months of storage.

Thus, the compounds belonging to group-2 formed a glassy state which was easy to crystallize by heating or by preservation. Furthermore, the physicochemical stability of the glassy MOM depended on the inlet temperature of the spray drying, in a similar manner as reported previously for MAT, and it was found that different glassy states were obtained by changing the inlet temperature of the spray drying.

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