Melting Granulation by Addition of Polyethyleneglycol for Stabilization of TAT-59[1-3]

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Compatibility of (*E*)-4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-(4-isopropylphenyl)-1-butenyl]phenyl monophosphate, TAT-59, with excipients was studied by using a powder mixture, a tablet obtained by compressing the powder mixture and powder obtained by crushing the tablet. TAT-59 with excipients of kinds of cellulose, sugar and starch degraded, whereas TAT-59 with polyethyleneglycol 6000 (PEG6000) was stable. Stability of the tablet consisting of TAT-59 and microcrystalline cellulose (MCC) obtained by the direct compression method (T-TM), the tablet consisting of TAT-59, MCC and PEG6000 by the direct compression method (T-TMP) and the tablet consisting of TAT-59, MCC and PEG6000 by the melting granulation method (T-MG) was evaluated by determining the formation of its hydrolysis product, DP-TAT-59. The degradation rate decreased in the order: T-TM > T-TMP > T-MG.

Thus, the melting granulation method with the addition of PEG6000 was found to stabilize the tablet containing TAT-59. The reason for the stabilization was presumably that the contact between TAT-59 and the water vapor or the water in MCC was decreased by coating the surface of TAT-59 and MCC with PEG6000, and that the phosphate group of TAT-59 was stabilized for the hydrogen bonding with PEG6000. Furthermore, the water-soluble PEG6000 little affected the dissolution profile of TAT-59, showing the melting granulation method can be useful for the stabilization of TAT-59.

Key words TAT-59; polyethyleneglycol; stabilization; melting granulation method; interaction

In a melting granulation, the granule is prepared by heating and it is not necessary to add a solution. Lipophilic wax is often used in granulation as the melting agent, and this preparation is applicable to a controlled release system.[4-6] There has been little reported on the stabilization of a drug by the melting granulation method using the water-soluble polyethyleneglycol 6000 (PEG6000).

TAT-59[7,8] (melting point, 205—210 °C) degrades to its hydrolysis product, DP-TAT-59, and phosphoric acid. We reported that the degradation of TAT-59 was affected by the water content,[9] the internal structure of the tablets[10] and the crystallinity.[2]

In this report, the compatibility of TAT-59 with excipients was studied for stabilization, and it was found that the addition of PEG6000 stabilized TAT-59. Tablets consisting of TAT-59, microcrystalline cellulose (MCC) and PEG6000 were prepared by the melting granulation method, and the utility of this technique was studied by comparison of its dissolution profile and stability.

Experimental

Materials TAT-59 (mean particle diameter 1.6 μm obtained by an air permeability method) was synthesized in our institute. Microcrystalline cellulose (Avicel PH-101, mean particle diameter 4.6 μm obtained by an air permeability method) and polyethyleneglycol 6000 (PEG, melting point about 58 °C, mean particle diameter 86.3 μm obtained by a sieving method) were purchased from Asahi Chemical Industry Co., Ltd. and Nihon Yushi Co., Ltd., respectively. Analytical reagents were of special grade (Wako Pure Chemical Industries Co., Ltd.).

Preparation of Samples in Compatibility Study Powder mixture (PM): TAT-59 and excipients at a ratio of 1/9 were mixed by a mortar. Tablets obtained by compressing PM (T-PM): PM was compressed by a tableting instrument (Riken Seiki Co., Ltd.) equipped with flat punches of 10.0 mm diameter at 1900 kg/cm^2.

Powder obtained by crushing T-PM (P-TPM): T-PM was crushed by a mortar.

Preparation of Tablets Composed of TAT-59, MCC and PEG Tablets Consisting of TAT-59 and MCC Obtained by the Direct Compression Method (T-TM): The powder mixtures (280 mg) of TAT-59 and MCC in ratios of 1/10 and 1/13 were compressed by a tableting instrument (Riken Seiki Co., Ltd.) equipped with flat punches of 10.0 mm diameter at 1900 kg/cm^2.

Tablets Consisting of TAT-59, MCC and PEG Obtained by the Direct Compression Method (T-TMP): The powder mixture (280 mg) of TAT-59, MCC and PEG in a ratio of 1/9/1 was compressed in a similar manner as T-TM.

Tablets Consisting of TAT-59, MCC and PEG Obtained by the Melting Granulation Method (T-MG): Forty g of the powder mixtures of TAT-59, MCC and PEG in ratios of 1/9/1, 1/9/2, 1/9/4 and 1/9/6 was placed in an 1 l-beaker in a thermostat and granulated at a heating temperature of 54—75 °C for 2—12 min by a stirrer (500 rpm, BL1200, HEDON), and PEG was allowed to adhere at room temperature. After sieving less than 1000 μm (the ratio of granules sieved at more than 1000 μm was less than 5% in every sample), granules (280 mg) were compressed in a similar manner as T-TM.

Observation of the Shape and Surface of Granules A scanning electron microscope (Model 2300, Hitachi Co., Ltd.) was used to observe the shape and surface of the granules.

IR Spectra IR spectra were obtained with a spectrophotometer (FT-IR Spectrometer 1720X, Perkin Elmer Co., Ltd.) by the KBr disk method.

Determination of DP-TAT-59 Content The amount of DP-TAT-59 was determined by high-performance liquid chromatography (HPLC), using the equipment previously described.[10]

Dissolution Study The dissolution profiles of a powder and granules containing 20 mg of TAT-59 equivalent were determined by the paddle method (JP XII), using 900 ml of phosphate buffer solution, pH 7.4, as the test solution at 37 °C and stirring at 100 rpm. Ten ml of each solution was pipetted through a membrane filter (0.45 μm pore size, Millipore). The concentration of TAT-59 was determined spectrophotometrically at 240 nm.

Storage Conditions The samples were kept at 50 °C in a desiccator containing a saturated solution of sodium bromide to maintain 50% relative humidity (RH).

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Results and Discussion

Compatibility Study of TAT-59 with Excipients Figure 1 shows the compatibility studies of TAT-59 with excipients kept at 50 °C under 50% RH. The amounts of DP-TAT-59 in the mixtures of TAT-59 and excipients except PEG were larger than that of TAT-59 alone, and DP-TAT-59 tended to be large in the following order: celluloses of MCC, CMC-Ca and HPC (hydroxypropylcellulose) > sugars of lactose and sucrose > starches of cornstarch and HPS (hydroxypropylstarch). Further, the amounts of DP-TAT-59 were large in the following order: P-TPM > T-PM > PM. The amount of DP-TAT-59 in the samples containing PEG, in contrast, scarcely increased.

Comparison of the Stability of Tablets Prepared by Direct Compression and Melting Granulation Methods Figure 2 shows the amounts of DP-TAT-59 in T-TM, T-TMP and T-MG. In lessening order their amounts were T-MG < T-TMP < T-TM. The reason for this was presumably that the large particles of PEG in the T-TMP covered part of the surfaces of TAT-59 and MCC by the plastic deformation at compression, so DP-TAT-59 in T-TMP was smaller than that in T-TM. Since T-MG was prepared at 70 °C above the melting point of PEG, TAT-59 was thought to be more stabilized when the greater part of its surface and that of MCC in T-MG was coated with PEG than that in T-TMP.

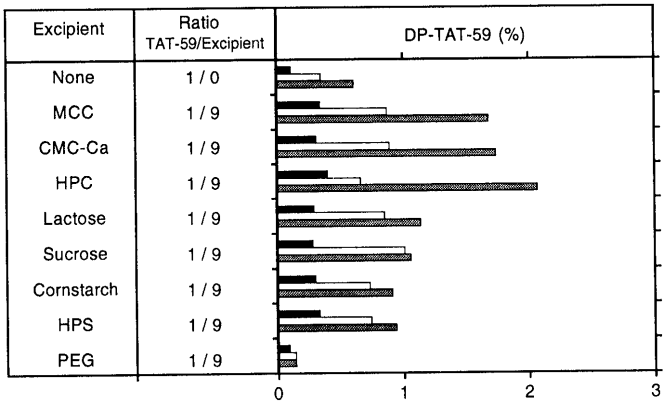


Fig. 1. Compatibility Studies of TAT-59 with Excipients at 50 °C under 50% RH for 4 Weeks

■, PM; □, T-PM; ■, P-TPM.

Conditions of the Melting Granulation DP-TAT-59 content in tablets prepared by the melting granulation method increased little. Therefore, the conditions of melting granulation were studied.

Figure 3 shows the particle diameter (D_{50}) of the granules and the hardness of the tablets prepared with them at a heating temperature of 70 °C for 2—12 min. The D_{50} and the hardness reached a constant level 2 min after the start of granulation.

Figure 4 shows the D_{50} of the granules and the hardness of tablets prepared with them at a temperature of 54—75 °C for 8 min. The D_{50} markedly increased and the hardness decreased with increasing temperature up to 65 °C.

Figure 5 shows scanning electron microscope (SEM) photographs of the granules prepared at a temperature of 54, 58 °C melting point of PEG, 65 and 70 °C for 8 min. In a) at 54 °C, the particles of TAT-59, MCC and PEG were observed, suggesting that no granulation had occurred. In b) at 58 °C, a mixture of particles and granules was visible. In c) at 65 °C and d) at 70 °C, the granules were observed without the particles. These facts indicate that the interparticles are bridged and the surfaces of the

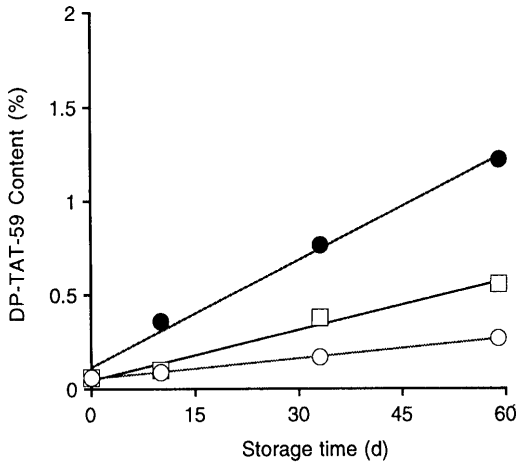


Fig. 2. Time Courses of Change in DP-TAT-59 Content of TAT-59 Tablets at 50 °C under 50% RH

●, T-TM (TAT-59/MCC = 1/10); □, T-TMP (TAT-59/MCC/PEG = 1/9/1); ○, T-MG (TAT-59/MCC/PEG = 1/9/1) prepared at a heating temperature of 70 °C.

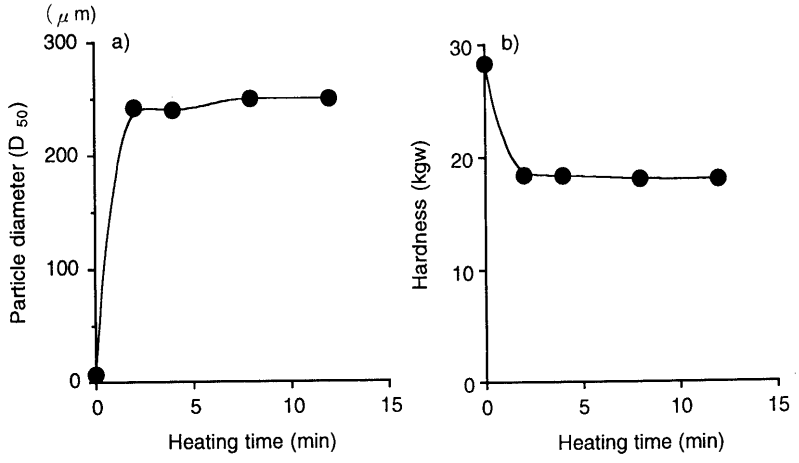


Fig. 3. Effect of Heating Time on Particle Size (a) and Hardness (b) of T-MG (TAT-59/MCC/PEG = 1/9/4)

Heating temperature, 70 °C.

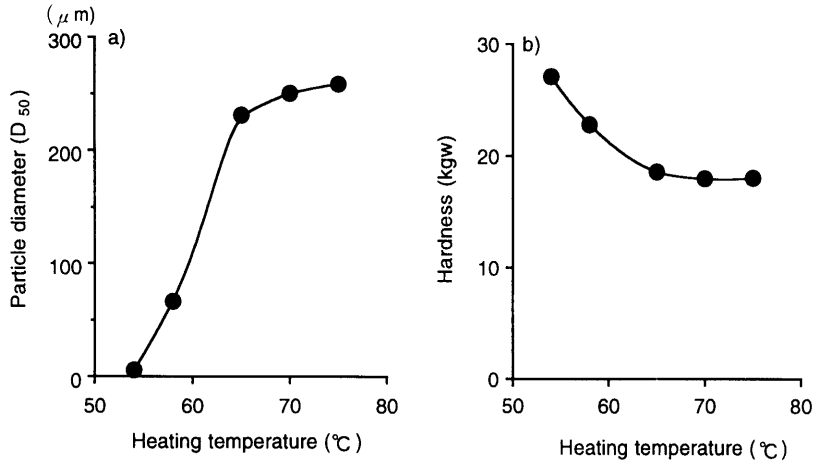


Fig. 4. Effect of Heating Temperature on Particle Size (a) and Hardness (b) of T-MG (TAT-59/MCC/PEG = 1/9/4)
Heating time, 8 min.

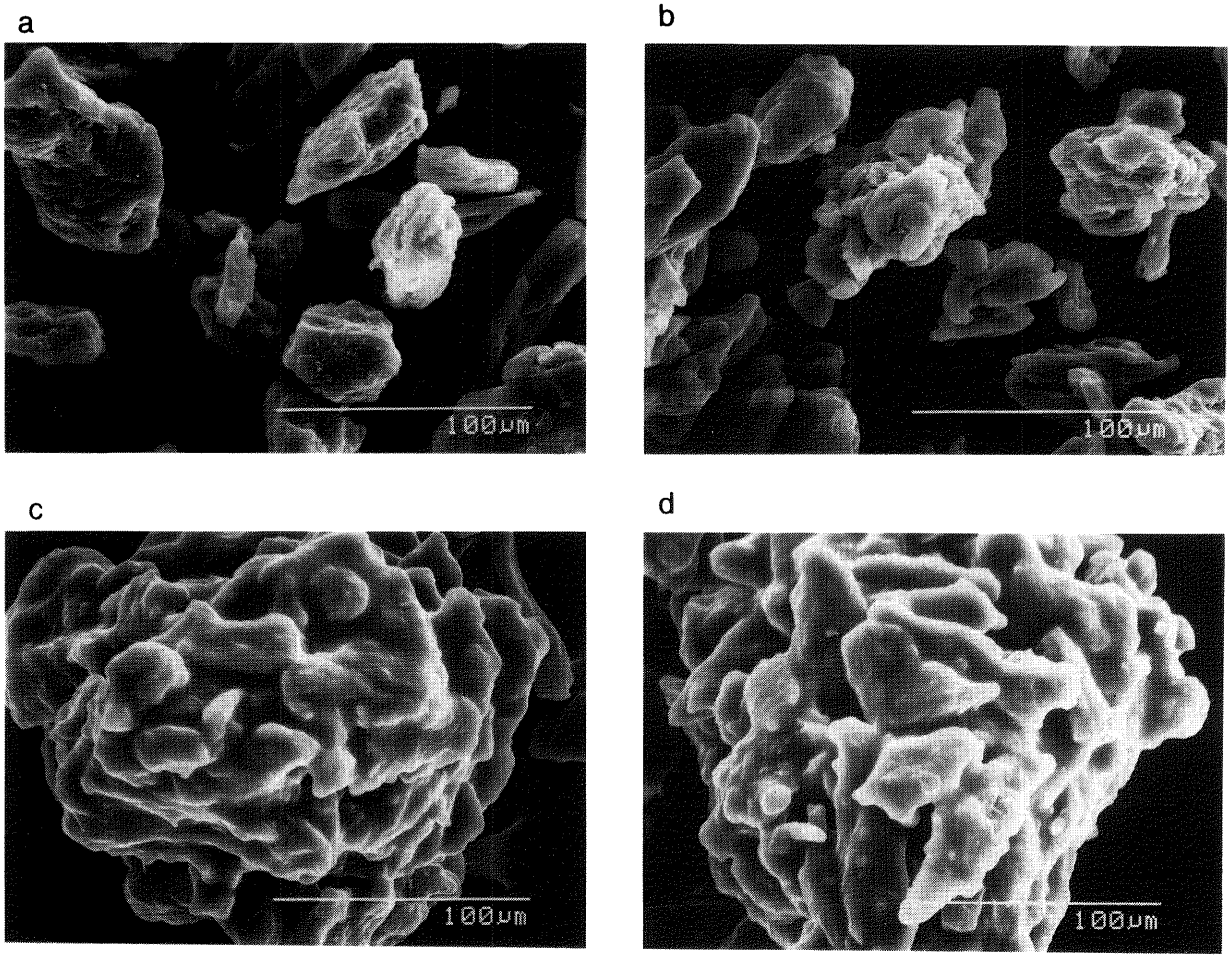


Fig. 5. SEM Photographs of Granules Obtained by Melting Granulation
Heating temperature: a) 54 °C, b) 58 °C, c) 65 °C, d) 70 °C.

granules are coated by PEG. From the results of the D_{50} and the hardness in Fig. 4, the shapes and surfaces of the granules in c) and d) were speculated to be similar to those of the granules prepared with more than 2 min of heating time. The surfaces of the granules prepared by the melting granulation method at above the melting point of PEG for more than 2 min are coated by PEG and the granule binding force is that of PEG-PEG, so that the hardness of their tablet may be weakened.

Figure 6 shows the amounts of DP-TAT-59 in T-TM, T-TMP and T-MG kept at 50 °C under 50% RH for 60 d. The increment in T-TM and T-TMP was 1.3% and 0.3—0.5%, respectively, while that in T-MG at every ratio was 0.2% and scarcely increased at all. Tableting with

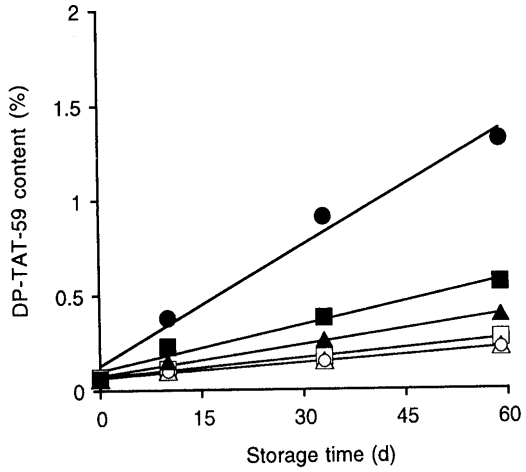


Fig. 6. Effect of Ratio of PEG on DP-TAT-59 Content in T-TMP and T-MG

T-TM (TAT-59/MCC = 1/13 ●); T-TMP (TAT-59/MCC/PEG = 1/9/1, ■; 1/9/4, ▲); T-MG (TAT-59/MCC/PEG = 1/9/1, □; 1/9/4, △; 1/9/6, ○).

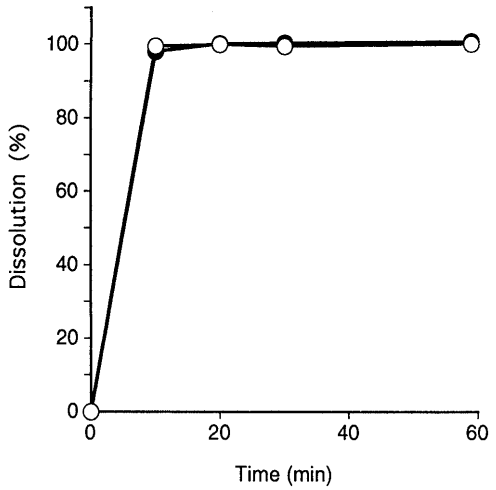
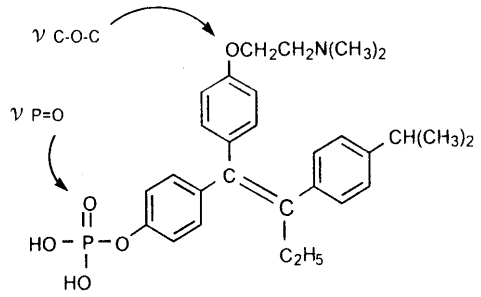
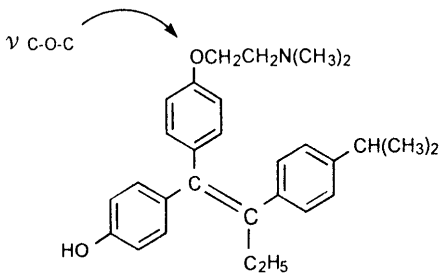


Fig. 7. Effect on Dissolution Profiles of TAT-59 in Melting Granulation

●, Powder mixture of TAT-59 and MCC (1/9); ○, granules consisting of TAT-59, MCC and PEG (1/9/2) prepared by the melting granulation method.

Table 1. Assignment of P=O and C–O–C Absorption in IR Spectrum of TAT-59 and DP-TAT-59

	Excipients	Wavelength (cm^{-1})
	TAT-59	1237
	TAT-59 + PEG	1227
	TAT-59 + MCC	1237
	TAT-59 + lactose	1237
	TAT-59 + cornstarch	1237
	DP-TAT-59	1237
	DP-TAT-59 + PEG	1237

granules prepared by the melting granulation method to which more than about 9% of PEG was added to the powder mixture of TAT-59 and MCC at a ratio of 1/9 improved the stability of the TAT-59 tablet.

Dissolution Study Figure 7 shows the dissolution profiles of the powder mixture of TAT-59 and MCC, and granules composed of TAT-59, MCC and PEG prepared by the melting granulation method. Since the two profiles are almost equal, the melting granulation using water-soluble PEG does not affect the dissolution of TAT-59. T-TM, T-TMP and T-MG containing excess MCC did not disintegrate for more than 30 min, so the powder mixture and granules prepared by the melting granulation method were used in the dissolution test.

Interaction of TAT-59 and PEG Table 1 shows the assignment of P=O and C–O–C absorption in the IR spectra of TAT-59 and DP-TAT-59. The absorption at 1237 cm^{-1} on the IR spectra of TAT-59 was assigned to P=O stretching and C–O–C stretching. In the granules consisting of TAT-59 and PEG (1/1) prepared by the melting granulation method, this stretching band was shifted to a lower wave number and appeared at 1227 cm^{-1}, while in granules consisting of DP-TAT-59, not containing a phosphate group, and PEG (1/1) prepared by the same method, the band appeared at 1237 cm^{-1} and was not shifted. These results suggest that the shift of the stretching band is due to the hydrogen bonding between the phosphate group of TAT-59 and PEG, and that DP-TAT-59 in T-MG decreases to stabilize the phosphate group of TAT-59. In the samples of TAT-59 with ex-

cipients of MCC, lactose and cornstarch, this stretching band appeared at 1237 cm^{-1} and was not shifted.

Conclusion

It was found that the melting granulation method with the addition of PEG decreased the hydrolysis product of TAT-59. The reason for the stabilization of TAT-59 was presumably that the contact between it and the water vapor or the water in MCC was lowered when the surface of TAT-59 and MCC was coated with PEG, and that the phosphate group of TAT-59 was stabilized by the hydrogen bonding with PEG. Furthermore, the melting granulation method by PEG only slightly affected the dissolution profile of TAT-59, which indicates this technique can be useful to stabilize TAT-59.

References and Notes

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