# Effects of Grinding and Tableting on Physicochemical Stability of an Anticancer Drug, TAT-59[1-3]

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**The effects of grinding and tableting on the physicochemical stability of TAT-59, (*E*)-4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-(4-isopropyl)phenyl]-1-butenyl]phenyl monophosphate, were studied. The crystallinity of TAT-59 ground in a planetary ball mill for 0—120 min or compressed at 0—4500 kg/cm$^2$ was evaluated by X-ray diffraction analysis and differential scanning calorimetry (DSC). The surface of TAT-59 was measured under a scanning electron microscope (SEM). The physicochemical stability of TAT-59, ground or compressed, was determined by measurements of water content, crystallinity and the amount of hydrolysis product, DP-TAT-59, formed. The crystallinity of ground TAT-59 decreased with increasing grinding time, and the amount of DP-TAT-59 increased with decrease in the crystallinity. Similar to ground TAT-59, the crystallinity of TAT-59 tablet gradually decreased with increasing compression pressure, and the amount of DP-TAT-59 tended to increase with decreasing crystallinity. These findings suggested that the decrease of the crystallinity of TAT-59 by mechanical force, such as grinding and tableting, raised the drug's reactivity and affected its stability.**

**Key words** stability; crystallinity; compression pressure; grinding; water content

In the formulation of a tablet, studies on the crystallinity of a bulk drug are important, because the crystallinity of the drug may be degraded by mechanical forces such as grinding, blending, drying and compressing. Decrease in the crystallinity often affects the physicochemical properties, stability, dissolution and bioavailability. Many researchers have reported the effects of grinding on the crystallinity of various drugs.[4-9] However, information concerning the effect of compression on the physicochemical stability and the crystallinity is limited.[10,11]

TAT-59[12,13] is a new drug for the treatment of breast cancer. It has a molecule of crystallization water and water content of 3.6%. The melting point of the drug is 205—210 °C and it is practically insoluble in water ($1.0 \times 10^{-3}$ mg/ml at 20 °C). TAT-59 degrades to its hydrolysis product, DP-TAT-59, and phosphoric acid as shown in Fig. 1 at a high temperature and high relative humidity (RH). We reported[2] that the degradation of TAT-59 in tablets was related to water content and was affected by the internal structure of the tablets, *e.g.* pore size.

Here, the effects of grinding and tableting on the crystallinity and the stability of TAT-59 were studied.

## Experimental

**Materials** TAT-59 was supplied by Taiho Fine Chemical Co., Ltd. Analytical reagents were of special grade (Wako Pure Chemical Industries Co., Ltd.).

**Preparation of Intact TAT-59, Ground TAT-59 and TAT-59 Tablet** Intact TAT-59: TAT-59 bulk was crushed by a sample-mill (KIIW-1; Fuji Sangyo Co., Ltd.).

Ground TAT-59: Intact TAT-59 was ground in an agate-made planetary ball mill (Model P-5; Fritsch Japan Co.), whose turning velocities of a supporting disk and bowls were about 202 and 436 rpm, respectively. Samples were taken out at appropriate intervals (10, 30 and 120 min).

TAT-59 Tablet: Intact TAT-59 (360 mg) was compressed at 500—4500 kg/cm$^2$ by the direct compression method using a multi-setting machine (AG-50kNE Shimadzu Seisakusyo, Ltd.) equipped with circular flat punches of 11.3 mm in diameter.

**Measurements** Surface Area and Particle Diameter: The surface areas and particle diameters of TAT-59 were determined by the air permeability method (SS-100 specific surface area meter, Shimadzu Seisakusyo, Ltd.).

Density: The densities of TAT-59 were determined by an air comparison pycnometer (Toshiba-Beckman Co., Ltd., Model 930).

Water Content: Tablets were crushed into a powder in a mortar, 0.3 g of which was used for measurement by Karl Fisher apparatus (MKA-3p, Kyoto Electric Co., Ltd.).

Amount of DP-TAT-59: Tablets were first crushed into a powder in a mortar and 10 ml of a mobile phase solution was added to a portion of the powder, equivalent to about 10 mg of TAT-59. The amount of DP-TAT-59 was determined by high-performance liquid chromatography (HPLC). The equipment used for HPLC was previously described.[2]

Analysis of Crystallinity: The crystallinity was calculated by the powder X-ray diffraction patterns with a diffractometer (Geigerflex RAD-IB, Rigaku, Ni-filter, Cu$K_\alpha$ ray; 40 kV; 20 mA) and was determined by Ruland's method.[14]

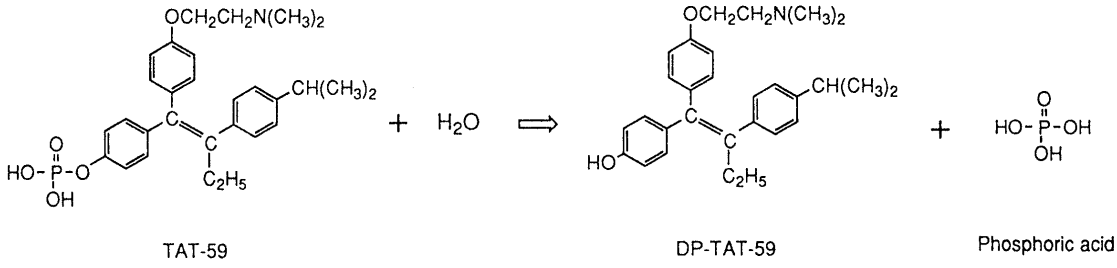


Fig. 1. Degradation of TAT-59

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Scanning Electron Microscopy: A scanning electron microscope (Model 2300, Hitachi Co., Ltd.) was used to examine the surface of TAT-59.

Thermal Analysis: Differential scanning calorimetry (DSC) curves were measured with a DSC instrument (TAS-100 and TG-8110, Rigaku Co., Ltd.) at the heating rate of 5 °C/min.

**Storage Conditions** The powder and the tablet were kept at 50 °C in a desiccator containing saturated salt (sodium chloride) solution to maintain 75% RH for 28 d. On specified days, water content, crystallinity and the amount of DP-TAT-59 were measured.

## Results and Discussion

**Effect of Grinding on the Surface Characteristics of TAT-59** Table 1 shows the surface areas and the particle diameters of intact TAT-59 and ground TAT-59 after various grinding times. The surface areas of TAT-59 decreased after more than 10 min of grinding, and the particle diameters increased. Figure 2 shows SEM photographs of intact and ground TAT-59; the particles seemed to form agglomerates when the grinding time exceeded 10 min. Compaction during the grinding process may cause this increase in particle diameter.

Table 1. Densities, Surface Areas, Particle Diameters and Crystallinities of TAT-59

| Grinding time (min) | Density[a] (g/ml) | Surface area[b] ($m^2$/g) | Particle diameter[b] ($\mu$m) | Crystallinity (%) |
|---|---|---|---|---|
| 0 | 1.21±0.01 | 2.64±0.01 | 1.9±0.0 | 44 |
| 10 | — | 0.86±0.00 | 5.8±0.0 | 33 |
| 30 | — | 0.86±0.11 | 5.7±0.1 | 20 |
| 120 | — | 0.90±0.00 | 5.5±0.0 | 9 |

*a*) Mean±S.D., $n=3$. *b*) Mean±S.D., $n=2$.

**Effect of Grinding and Compression on the Crystallinity of TAT-59** Figure 3 shows the powder X-ray diffraction patterns of TAT-59 after various grinding times; the peak positions of the ground drug are almost the same, so the crystalline form was not changed. The peak heights markedly decreased with increasing grinding time. Table I shows the values of crystallinity calculated by Ruland's method. The crystallinity of TAT-59 decreased with longer grinding time, and after 120 min of grinding the crystallinity was calculated as 9%, while no diffraction peaks of the drug were observable.

Figure 4 shows the relationship between compression pressure and crystallinity of TAT-59 tablets calculated by Ruland's method. Similar to ground TAT-59, the crystallinity of TAT-59 tablets gradually decreased with increasing compression pressure.

Figure 5 shows the DSC curves of intact and ground TAT-59. The endothermic peaks observed around 210 °C, and the exothermic peaks observed around 150 °C in the DSC curves of intact TAT-59 and ground TAT-59 were confirmed to be due to the fusion, and the crystallization, respectively. The heat of fusion decreased with increasing grinding time, and the heat of crystallization increased. Ground TAT-59 was not thought appropriate for crystallizing at the heating rate of 5 °C/min in DSC; therefore, the heat of fusion of ground TAT-59 was smaller than that of intact TAT-59. These X-ray diffraction patterns and the DSC curves indicated that the crystallinity of TAT-59 decreased with increasing grinding time in a planetary ball mill and that of ground TAT-

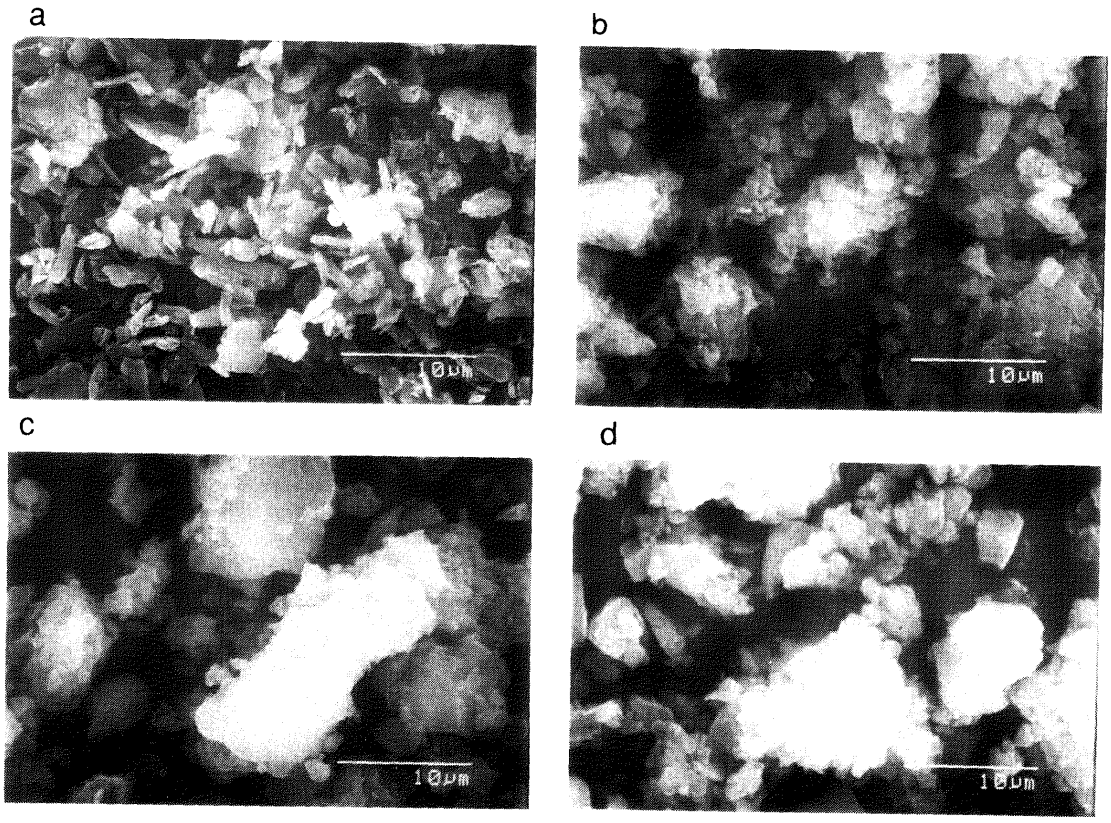


Fig. 2. Scanning Electron Micrographs of TAT-59
Grinding time: a, 0 min; b, 10 min; c, 30 min; d, 120 min.

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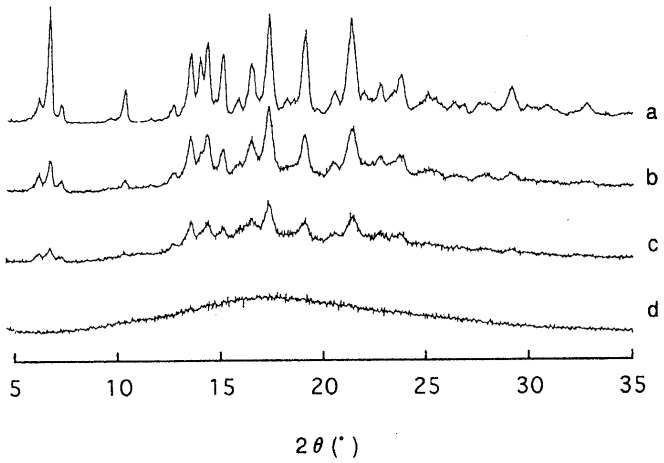


Fig. 3. Effect of Grinding on X-Ray Diffraction Patterns of TAT-59
Grinding time: a, 0 min; b, 10 min; c, 30 min; d, 120 min.

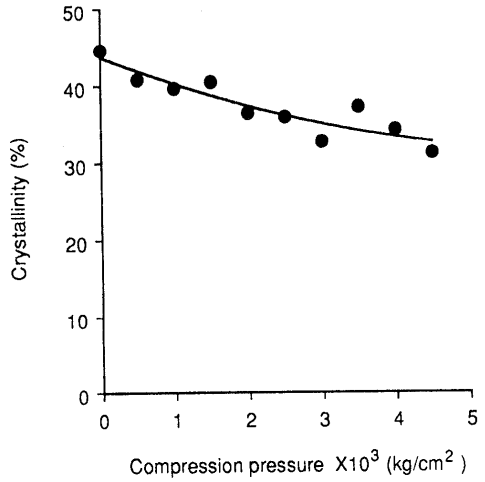


Fig. 4. Relationship between Compression Pressure and Crystallinity of TAT-59

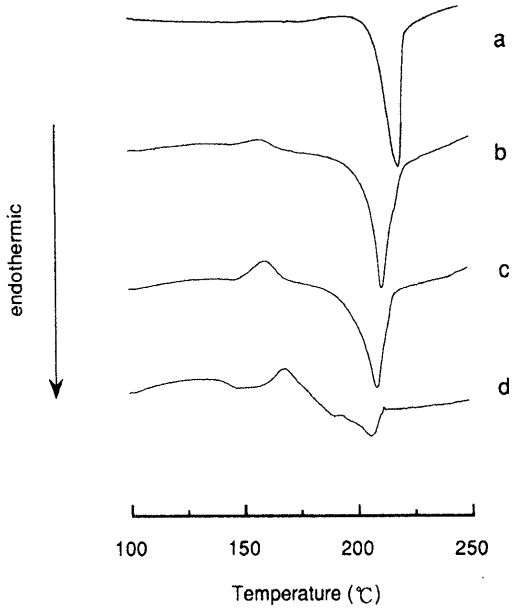


Fig. 5. Effect of Grinding on DSC Curves of TAT-59
Grinding time: a, 0 min; b, 10 min; c, 30 min; d, 120 min.

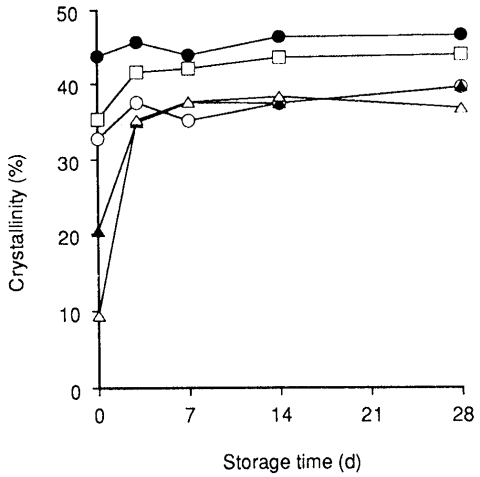


Fig. 6. Time Course of Change in Crystallinity of Intact TAT-59, Ground TAT-59 and TAT-59 Tablet at 50 °C under 75% RH
Intact TAT-59, ●; ground TAT-59: 10 min (○), 30 min (▲), 120 min (△); TAT-59 tablet, 4500 kg/cm² (□).

59 for 120 min became nearly amorphous.

**Effect of Grinding and Compression on the Stability of TAT-59** The solid state stabilities of ground TAT-59 and TAT-59 tablet were studied at 50 °C under 75% RH. Figure 6 shows the time course of change in crystallinity of the drug calculated by Ruland's method. Initial crystallinity of intact TAT-59 and ground TAT-59 for 10, 30 and 120 min were 44, 33, 20 and 9%, respectively. Intact TAT-59 was fairly stable during 28 d, while ground TAT-59 was recrystallized in 3 d. Figure 6 also shows the time course of changes in the crystallinity of TAT-59 tablet compressed at 4500 kg/cm². Similar to ground TAT-59, the tablet was recrystallized in 3 d. According to a recent report,[8] the recrystallization of amorphous ursodeoxycholic acid occurred immediately under conditions of high humidity. The recrystallization of amorphous TAT-59 in this study was also attributed to such a moisture effect. These findings suggested that the crystal structure of ground TAT-59 and TAT-59 tablet quickly recombined, and that this increased crystallinity resulted in the stabilization of TAT-59.

Figure 7 shows the time course of changes in the amount of DP-TAT-59; increased grinding time raised DP-TAT-59 content in both the intact and ground drug. From the beginning to 3 d, ground TAT-59 quickly degraded, and on and after 3 d, the DP-TAT-59 content gradually increased. Rise in crystallinity may raise the stability of TAT-59.

On the other hand, the initial water content of intact TAT-59 and ground TAT-59 was about 3.7%. That of the former scarcely changed during 28 d, while that of the latter increased slightly with increase in grinding time and equilibrated in 3 d. The equilibrated water content of intact TAT-59 and ground TAT-59 for 10, 30 and 120 min were 3.7, 4.0, 4.3 and 4.7%, respectively.

In Fig.7, the DP-TAT-59 content in TAT-59 tablets compressed at 500—4500 kg/cm² increased slightly during 28 d, then tended to continue to increase as compression pressure rose.

**Relationship between Crystallinity and Stability** Figure 8 shows the relationship between initial crystallinity and the amount of DP-TAT-59 in intact TAT-59, ground

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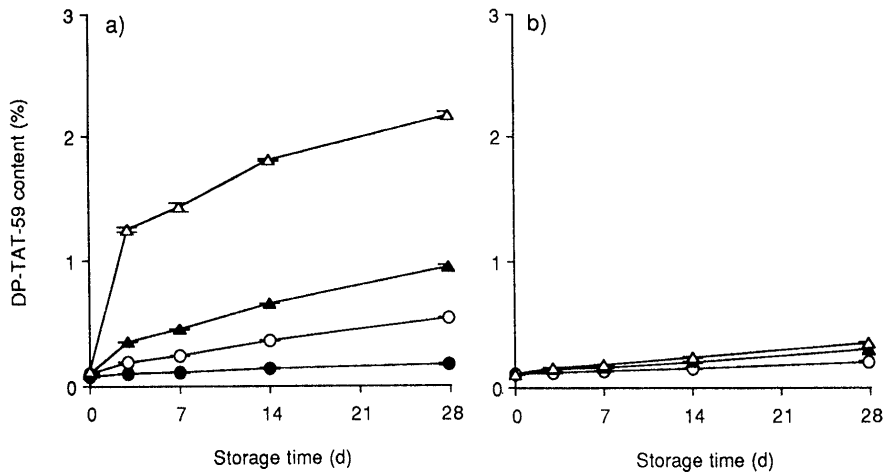


Fig. 7. Time Course of Change in DP-TAT-59 Content of Intact TAT-59 (a), Ground TAT-59 (a) and TAT-59 Tablet (b) at 50 °C under 75% RH

Intact TAT-59, ●; ground TAT-59: 10 min (○), 30 min (△) and 120 min (▲); TAT-59 tablet: 500 kg/cm$^2$ (○), 1500 kg/cm$^2$ (▲), 4500 kg/cm$^2$ (△). Each point represents the mean ± S.D. (each symbol includes S.D.).

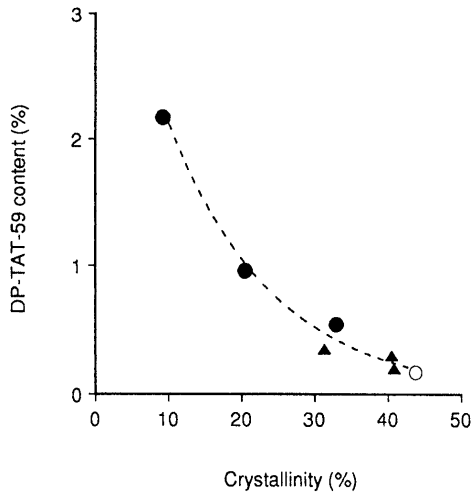


Fig. 8. Relationship between Crystallinity and DP-TAT-59 Content after 28 d

Intact TAT-59, ○; ground TAT-59, ●; TAT-59 tablet, ▲.

TAT-59 and TAT-59 tablet after 28 d. In ground TAT-59, DP-TAT-59 increased with decrease in initial crystallinity. While the amount in the tablet after 28 d was minimal, it also tended to rise with decreasing initial crystallinity.

Because TAT-59 is an amphoteric molecule containing a dimethylamino group and a phosphoric group, the bonding force of the TAT-59 crystal structure may be based largely on the intermolecular hydrogen bonds, and the reduction in crystallinity by grinding or tableting may weaken the bonding force of the structure. These findings suggested that the decrease of the crystallinity of TAT-59 by mechanical force, such as the grinding or tableting process, raised its reactivity and affected its stability.

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