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Effects of Compression Pressure on Physical and Chemical Stability of Tablets Containing an Anticancer Drug TAT-59[1-3)]

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(*E*)-4-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]-2-(4-isopropyl)phenyl]-1-butenyl]phenyl monophosphate (TAT-59) is a new drug for the treatment of breast cancer. Physical and chemical stability of mixtures of TAT-59 and microcrystalline cellulose (1 : 9) compressed at 0, 300, 600 and 1400 kg/cm^2 was evaluated by determination of water content, porosity and the amount of hydrolysis product, DP-TAT-59, formed.

The water contents and porosity of these tablets scarcely changed during 57 d at 25—60 °C under 50 % relative humidity (RH). The degradation rate of TAT-59 increased with increasing compression pressure as well as temperature. The apparent activation energy and frequency factor were determined from an Arrhenius plot of the degradation rate. Activation energy of these tablets was almost the same, while the frequency factor tended to increase with increasing compression pressure. The porosity and pore sizes in TAT-59-containing tablets decreased with increasing compressive force. We speculated from these observations that the increase in compression pressure decreased the distance and increased the contact area between TAT-59 and microcrystalline cellulose. The proximity between TAT-59 and moisture presented at the surface of microcrystalline cellulose by compression was considered to enhance the degradation of TAT-59.

Keywords stability; compression pressure; pore size; water content; breast cancer

In the formulation of a tablet, it is important to determine the interactions between the drug and excipients in the solid state. Many researchers have reported the effects of water content and the interaction with excipients on the stability of various drugs.[4-13)] Compression is necessary for appropriate mechanical strength in tablets and may affect the stability of the drug, and compression pressure is known to be correlated with change of internal structure of a tablet. However, information concerning the relationship between internal structure and the stability of tablets is limited.

TAT-59[14,15)] is a new drug for the treatment of breast cancer. It has a molecule of water of crystallization and its water content is 3.6% in the calculation. Melting point of the drug is 205—210 °C and it is practically insoluble in water (1.0×10^{-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 high temperature and relative humidity (denoted as RH). DP-TAT-59 is effective against breast cancer, but becomes inert by gastric acid. Therefore, TAT-59 must be stabilized when used in tablets. We earlier reported[2)] that the degradation of TAT-59 in tablets was related to water content and was accelerated by compression and addition of excipients.

In the present study, we compared physical and chemical stabilities of tablets consisting of TAT-59 and microcrystalline cellulose (1 : 9) compressed at various pressures. Further, the relationship between the degradation of TAT-59 and internal structure of the tablets, *e. g.* pore size, is discussed.

Experimental

Materials TAT-59 was supplied by Taiho Fine Chemical Co., Ltd. Microcrystalline cellulose (Avicel PH-101) was from Asahi Chemical Industry Co., Ltd. The particle diameters of TAT-59 and microcrystalline cellulose measured by the air permeability method and the densities measured by an air comparison pycnometer (Toshiba-Beckman Co., Ltd., Model 930) are shown in Table I. Analytical reagents were of special grade (Wako Pure Chemical Industries Co., Ltd.).

Preparation TAT-59 and microcrystalline cellulose (MCC) were mixed at a ratio of 1 : 9 (MCC-pow). MCC-pow (360 mg) was compressed at 300, 600 and 1400 kg/cm^2 by the direct compression method using a multi-setting machine (TCM-5000C Minebea Co., Ltd.) equipped with circular flat punches 11.3 mm in diameter (MCC-tab).

Measurement 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

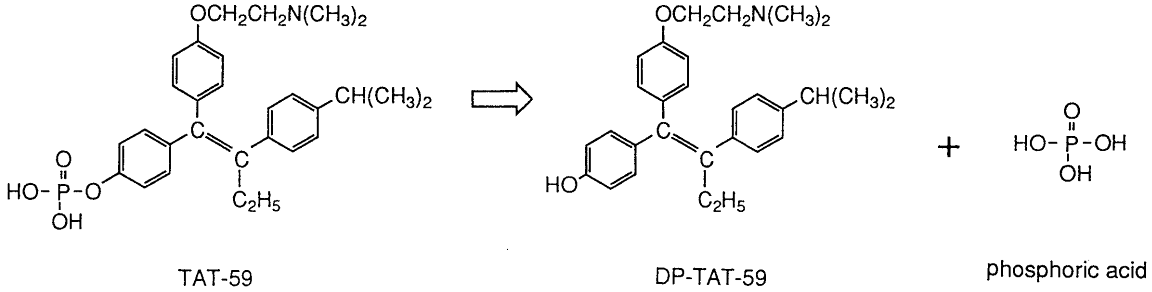

Fig. 1. Degradation of TAT-59

the powder, equivalent to about 10 mg of TAT-59. The amount of DP-TAT-59 was determined by high-performance liquid chromatograph (HPLC) equipped with an ODP (octadecyl groups bonded to polymers) column (5 μm, 150 × 4.6 mm ; Showa Denko Co., Ltd.). The HPLC equipment consisted of a JASCO-800 and an 875-UV spectrophotometer (Japan Spectroscopic Co., Ltd.). The absorbance at 240 nm for TAT-59 and DP-TAT-59 was measured. The mobile phase solution consisted of acetonitrile and an aqueous solution (pH 11.0) containing 5 mM Na_2SO_4, 10 mM cetyltrimethylammonium chloride and 10 mM Na_3PO_4 (55 : 45).

Porosity: The densities of TAT-59 and MCC measured with the air comparison pycnometer are shown in Table I. The porosity of each tablet was determined by measuring its weight, diameter, thickness and density.

Pore Size Distribution: The pore size in each tablet was measured by mercury intrusion porosimetry (Quantachrome Co., Autoscan-33). The principle of mercury intrusion porosimetry is as follows: when mercury is forced into a pore in a solid material, the relationship between the pressure required to fill the pore completely and the size of the pore is expressed by Washburn's equation[16]:

$$Pr = -2\phi \cos \theta \qquad (1)$$

where P is the pressure; r, the pore radius; ϕ, the surface tension of mercury and θ, the contact angle of mercury with the solid material. When ϕ and θ were regarded as 480 dyn/cm and 140°, respectively, Eq. 1 was reduced to the following Eq. 2,[17]

$$D = 213/P \qquad (2)$$

where D is the pore diameter in microns and P is the absolute pressure in psia.

Analysis of Crystallinity of TAT-59 Powder: The crystallinity of TAT-59 powder was analyzed by the powder X-ray diffraction patterns with a diffractometer (Geigerflex RAD-IB, Rigaku, Ni-filter, CuK_α ray; 40 kV; 20 mA).

Storage Conditions The powder and the tablet were kept at 25, 40, 50 or 60 °C in desiccators containing saturated salt solutions[18] to maintain 50% relative humidity (RH) for 57 d (Table II). On specified days, water content, porosity and the amount of DP-TAT-59 were measured.

Results and Discussion

Figure 2 shows time courses of changes in water content of MCC-pow and MCC-tabs kept at 25—60 °C under 50%RH for 57 d. Initial water contents of MCC-pow and MCC-tabs were similar (about 5.0%), changed little during the 57 d, and were independent of the compression pressure (0—1400 kg/cm^2). The water content slightly increased with decreasing temperature.

The time courses of changes in porosity of three kinds of MCC-tabs kept at various temperatures are shown in Fig. 3. Initial porosity of MCC-tabs at 300, 600 and 1400 kg/cm^2 were 0.38, 0.26 and 0.11, respectively, and these values changed little during the 57 d, at any temperature, although porosity decreased with increasing compression pressure.

Figure 4 shows the time courses of changes in the amounts of DP-TAT-59 in MCC-pow and MCC-tabs. The amount in each sample increased with increasing compression pressure as well as temperature. The increments of DP-TAT-59 in MCC-pow and MCC-tab at 300, 600

TABLE I. Particle Diameter and Density of Powders Used

	TAT-59	Microcrystalline cellulose
Particle diameter (μm)[a)]	1.6 ± 0.01	4.6 ± 0.05
Density (g/ml)[a)]	1.21 ± 0.006	1.56 ± 0.002

a) Mean ± S.D., $n = 3$.

TABLE II. Relative Humidities of Salt Solutions Used at 25—60 °C

Salt	Temperature	Relative humidity
$Mg(NO_3)_2 \cdot 6aq$	25 °C	52.9% RH
$NaBr \cdot 2aq$	40 °C	52.4% RH
$NaBr \cdot 2aq$	50 °C	49.7% RH
$NaBr \cdot 2aq$	60 °C	49.9% RH

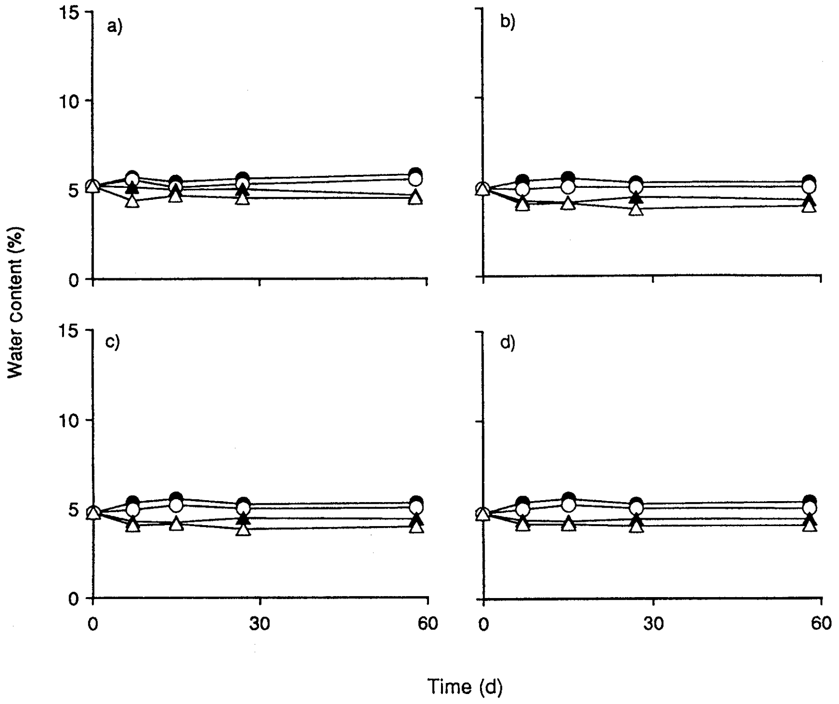

Fig. 2. Time Courses of Changes in Water Content of MCC-pow and MCC-tabs at Various Storage Temperatures under 50 %RH

Compression pressure: MCC-pow (a), 300 kg/cm^2 (b), 600 kg/cm^2 (c) and 1400 kg/cm^2 (d). Temperatures: 25 °C (●), 40 °C (○), 50 °C (▲) and 60 °C (△). Each point represents the mean ± S.D. (Each symbol includes S.D.).

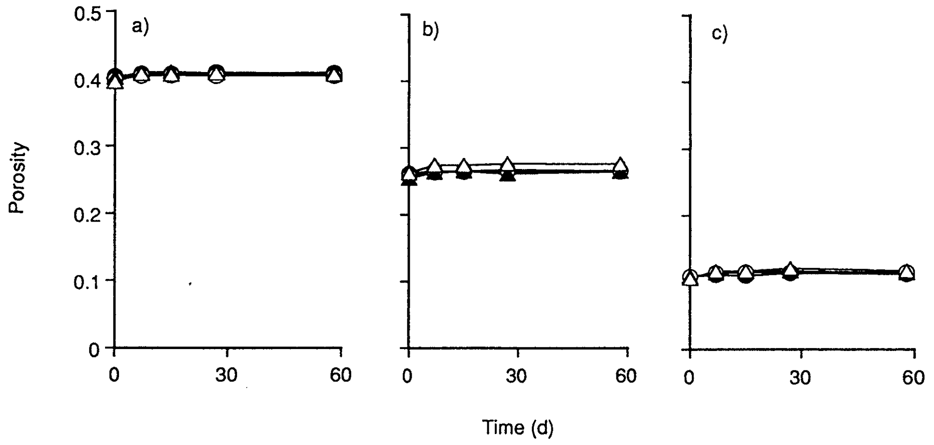

Fig. 3. Time Courses of Changes in Porosity of MCC-tabs at Various Storage Temperatures under 50%RH

Compression pressure: 300 kg/cm^2 (a), 600 kg/cm^2 (b) and 1400 kg/cm^2 (c). Temperatures: 25 °C (●), 40 °C (○), 50°C (▲) and 60 °C (△). Each point represents the mean ± S.D. (Each symbol includes S.D.).

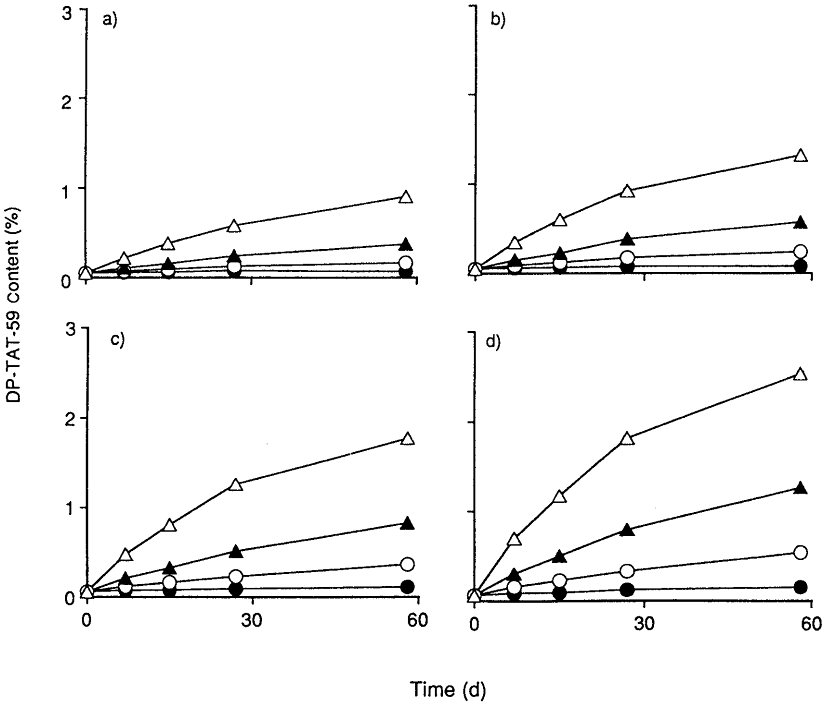

Fig. 4. Time Courses of Changes in DP-TAT-59 Content of MCC-pow and MCC-tabs Determined by Zero Order Kinetics at Various Storage Temperatures under 50%RH

Compression pressure: MCC-pow (a), 300 kg/cm^2 (b), 600 kg/cm^2 (c) and 1400 kg/cm^2 (d). Temperatures: 25 °C (●), 40 °C (○), 50 °C (▲) and 60 °C (△). Each point represents the mean ± S.D. (Each symbol includes S.D.).

and 1400 kg/cm^2 were 0.9, 1.2, 1.8 and 2.4%, respectively, when kept at 60 °C for 57 d. The amount of DP-TAT-59 in MCC-tabs increased with increasing compression pressure in the range of 0—1400 kg/cm^2. TAT-59 degraded to DP-TAT-59 and phosphoric acid, and so the water in MCC-tabs was thought to be increasingly acidic with greater amounts of DP-TAT-59. The solubility of TAT-59 decreased in the buffer solution below pH 7, because the pK_a of phosphoric group was 2.16 and 6.27. Therefore, the slope of the amount of DP-TAT-59 tended to be small with the elapse of time.

The degradation rates of MCC-pow and MCC-tabs were determined, assuming the initial degradation followed apparent zero-order kinetics as shown in Fig. 4; Arrhenius plots of these rates are shown in Fig. 5. Each plot was linear, and their apparent activation energy (E_a) and frequency factor (F_f) were calculated (Table III). The E_a of each MCC-tab was almost equal and independent of compression pressure, whereas the F_f tended to increase with increasing compression pressure (Fig. 6). The F_f of MCC-tab at 1400 kg/cm^2 was about 2.5 times that of MCC-pow.

The degradation rate was also analyzed by Jander's equation[19,20];

$$[1-(1-x)^{1/3}]^2=kt$$

where x denotes the rate of DP-TAT-59, k, rate constant; and t, time. Jander's plots were linear as shown in Fig. 7, and Arrhenius plots of the degradation rate determined by Jander's equation were also linear (Fig. 8). The E_a and F_f were calculated as shown in Table IV. Similar to the result determined by zero order kinetics, the E_a of MCC-tabs was almost equal, whereas the F_f tended to increase with increasing compression pressure except MCC-tab at 300 kg/cm^2. It was not clear why the E_a and F_f of MCC-tab at 300 kg/cm^2 calculated by Jander's equation were larger in value.

Since the water content in all MCC-tabs was identical throughout the experimental period as shown in Fig. 2, the effect of water content on the degradation were also believed to be almost equal. To determine the reason TAT-59 degradation was enhanced by compression, the internal structure of MCC-tabs was investigated.

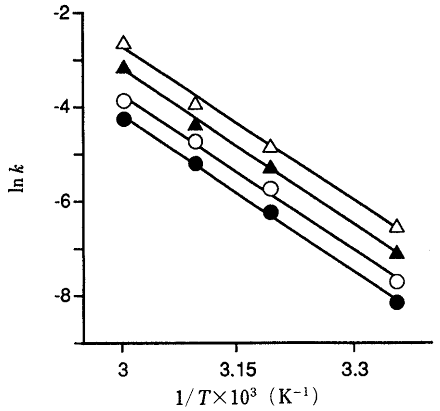

Fig. 5. Arrhenius Plots of Degradation Rates of MCC-pow and MCC-tabs Determined by Zero Order Kinetics

Compression pressure: MCC-pow (●), 300 kg/cm^2 (○), 600 kg/cm^2 (▲) and 1400 kg/cm^2 (△).

Figure 9 shows the relationship between compression pressure and porosity of MCC-tabs. Porosity decreased with increasing compression pressure and was maintained at about 0.1 at more than about 1000 kg/cm^2. Pore size distribution in MCC-tabs is shown in Fig. 10. The pore size decreased with increasing compression pressure, and

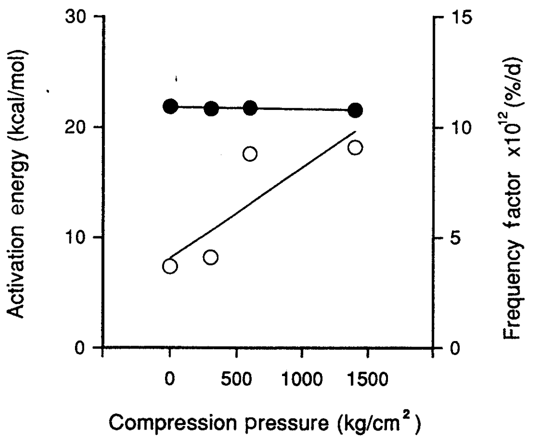

Fig. 6. Relationship between Compression Pressure and Activation Energy (●) or Frequency Factor (○) Determined by Zero Order Kinetics

Table III. Arrhenius Plots Determined by Zero Order Kinetics

Compression pressure (kg/cm^2)	Activation energy (kcal/mol)	Frequency factor (%/d)
0 (MCC-pow)	21.9	3.7×10^{12}
300 (MCC-tab)	21.7	4.1×10^{12}
600 (MCC-tab)	21.8	8.8×10^{12}
1400 (MCC-tab)	21.6	9.1×10^{12}

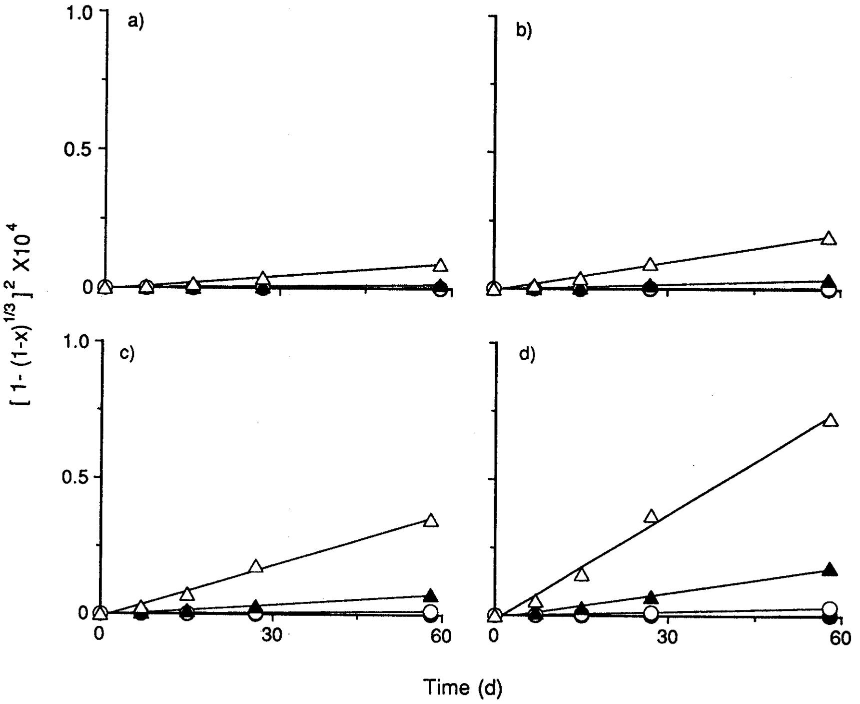

Fig. 7. Time Courses of Changes in DP-TAT-59 Content of MCC-pow and MCC-tabs Determined by Jander's Equation at Various Storage Temperatures under 50%RH

Compression pressure: MCC-pow (a), 300 kg/cm^2 (b), 600 kg/cm^2 (c) and 1400 kg/cm^2 (d). Temperatures: 25 °C (●), 40 °C (○), 50 °C (▲) and 60 °C (△). Each point represents the mean ± S.D. (Each symbol includes S.D.).

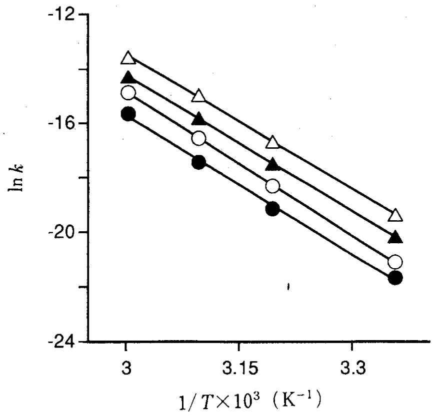

Fig. 8. Arrhenius Plots of Degradation Rates of MCC-pow and MCC-tabs Determined by Jander's Equation

Compression pressure: MCC-pow (●), 300 kg/cm^2 (○), 600 kg/cm^2 (▲) and 1400 kg/cm^2 (△).

Table IV. Arrhenius Plots Determined by Jander's Equation

Compression pressure (kg/cm^2)	Activation energy (kcal/mol)	Frequency factor (d^{-1})
0 (MCC-pow)	33.7	2.0×10^{15}
300 (MCC-tab)	(34.9)	(28.7×10^{15})
600 (MCC-tab)	33.1	3.3×10^{15}
1400 (MCC-tab)	32.9	5.1×10^{15}

the average pore sizes in MCC-tabs at 300, 600 and 1400 kg/cm^2 were 2.0, 0.7 and 0.3 μm, respectively. The distance between the particles of TAT-59 and MCC presumably also decreased with increasing compression pressure.

The crystallinity of tablets consisting of TAT-59 alone and MCC-tabs compressed at 0—2500 kg/cm^2 was analyzed by the powder X-ray diffraction method. The X-ray diffraction patterns were almost equivalent and independent of the compression pressure, so that compression hardly affected the crystallinity.

The degradation rate of TAT-59 and the water contents in MCC-pow, MCC-tab, the powder of TAT-59 alone, and the tablets of TAT-59 alone at 50 °C under 50%RH are shown in Table V. The degradation rate of TAT-59 tended to increase with compression in agreement with our previous report.[2)] The degradation rate of MCC-pow was about twice that of the powder of TAT-59 alone. The water adsorbed on MCC was considered to affect the degradation of TAT-59.

Ahlneck and Alderborn[13)] studied the water content of MCC and suggested that about 3 wt% of it was strongly bound in the region of amorphous cellulose, while the remaining water was less tightly bound and was present both in the amorphous region and at the surface of the particles. The less tightly bound water would affect the stability of the drug. They also reported that the degradation rate of aspirin decreased in the following order: binary mixture tablet consisting of aspirin and MCC (1 : 1) > two-layer tablet consisting of one layer of aspirin and one layer of MCC > tablet consisting of aspirin alone. The proximity between the aspirin and MCC particles was considered to enhance the degradation of aspirin due to moisture on the MCC surface.

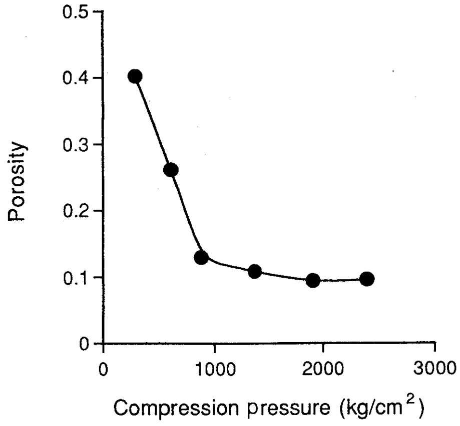

Fig. 9. Relationship between Compression Pressure and Porosity of MCC-tabs

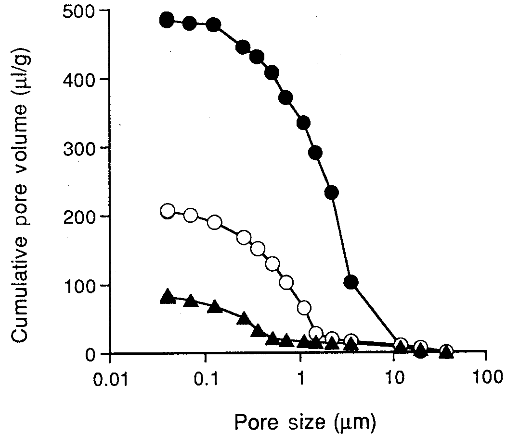

Fig. 10. Pore Size Distribution in MCC-tabs

Compression pressure: 300 kg/cm^2 (●), 600 kg/cm^2 (○) and 1400 kg/cm^2 (▲).

Table V. Equilibrium Water Content and Degradation Rate of TAT-59 at 50 °C under 50% RH

Sample	Water (%)[a)]	*k* (%/d)
Powder of TAT-59 alone[b)]	3.4	2.47×10^{-3}
Tablet of TAT-59 alone[b)] at 1700 kg/cm^2	3.4	1.06×10^{-2}
MCC-pow	5.0	5.52×10^{-3}
MCC-tab at 300 kg/cm^2	5.0	8.83×10^{-3}
MCC-tab at 600 kg/cm^2	5.0	1.29×10^{-2}
MCC-tab at 1400 kg/cm^2	5.0	2.00×10^{-2}

a) Equilibrium water content (at 57 d). *b)* The value is shown in our previous paper.[2)]

In the present study, we speculated that the decrease in distance between TAT-59 and MCC increased the contact area between water adsorbed on MCC and the phosphoric group of TAT-59. The tendency of the frequency factor to increase with increasing compression pressure was also interpreted as offering greater probability of contact between TAT-59 and MCC.

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