Effects of Water Content 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 a tablet consisting of TAT-59 powder and a few excipients (Formulated tablet), a tablet consisting of only TAT-59 powder (TAT-59 tablet) and TAT-59 powder itself was evaluated based on water content, tensile strength, porosity, the amount of TAT-59 and its hydrolysis product, DP-TAT-59.

The water content of Formulated tablet increased with relative humidity (RH), whereas that of TAT-59 tablet and TAT-59 powder scarcely changed. The equilibrium water content of Formulated tablet was much greater than that of the TAT-59 tablet or TAT-59 powder due to adsorbed moisture by the excipients. The tensile strength and porosity of Formulated tablet decreased and increased linearly, respectively, with increasing water content. The degradation rate of TAT-59 decreased in the following order: Formulated tablet>TAT-59 tablet>TAT-59 powder. The relationship between equilibrium water content and degradation rate of the Formulated tablet was determined by the Carstensen equation, in which the interaction order between the drug and water content was 1.9, and the degradation of TAT-59 in Formulated tablet was related to water content. Thus, it was found that the degradation of TAT-59 was accelerated by compression and addition of excipients.

Keywords breast cancer; stability; water content; porosity; tensile strength; Carstensen equation

The chemical stability of solid drugs in tablet form is influenced by the water content of the tablets.[4] Recently, the relationship between water content (or relative humidity (RH)) and degradation of water-soluble drugs (such as thiamine hydrochloride,[5] ascorbic acid[6] and propantheline bromide[7]) has been studied, but the effect of water content of a tablet containing a water-insoluble drug on its degradation is not yet clear.

(*E*)-4-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]-2-(4-isopropyl)phenyl]-1-butenyl]phenyl monophosphate (TAT-59)[8] is a new drug for breast cancer. Its melting point is 205—210 °C and it is practically insoluble in water (1.0×10^{-3} mg·ml^{-1} at 20 °C). TAT-59 degrades to its hydrolysis product, DP-TAT-59, and phosphate as shown in Fig. 1 at high temperature and RH. The effect of water content on degradation of a water-insoluble drug, TAT-59, in tablets with or without other ingredients should be determined.

In the present study, we compared physical (tensile strength and porosity) and chemical (the amount of TAT-59 and DP-TAT-59) stabilities of Formulated tablet, TAT-59 tablet and TAT-59 powder stored at various RH. The effects of water content of Formulated tablet on the tensile strength, porosity and degradation of TAT-59 are discussed.

Experimental

Materials TAT-59 bulk was supplied by Taiho Fine Chemical Co., Ltd. Lactose was purchased from Meggle Co., Ltd. Microcrystalline cellulose (Avicel PH-101) was from Asahi Chemical Industry Co., Ltd. Hydroxypropylstarch (HPS-101) was from Freund Sangyo Co., Ltd. Magnesium stearate was from Taihei Chemical Industry Co., Ltd. Analytical reagents were of special grade (Wako Pure Chemical Industries, Ltd.).

Preparation of TAT-59 Powder, TAT-59 Tablet and Formulated Tablet TAT-59 Powder: TAT-59 bulk was crushed by Sample-mill (KIIW-1; Fuji Sangyo Co., Ltd.).

TAT-59 Tablet: TAT-59 powder (360 mg) was compressed by a multisetting machine (TCM-5000C Minebea Co., Ltd.) equipped with a circular flat punch of 11.3 mm diameter at 1700 kg·cm^{-2}.

Formulated Tablet: TAT-59 powder and excipients shown in Table I were stirred with 280 ml·kg^{-1} of water by an agitation granulator (PK-250; Freund Sangyo Co.). The granule was dried in a fluidized bed drier (FL-MINI; Freund Sangyo Co.). After adding magnesium stearate to the granule, it was compressed by a rotary tableting machine (Kikusui

TABLE I. Formulation of Formulated Tablet

TAT-59	2.8%
Excipients	96.6%
A mixture of lactose, microcrystalline cellulose and hydroxypropylstarch (2:1:1)	
Magnesium stearate	0.6%

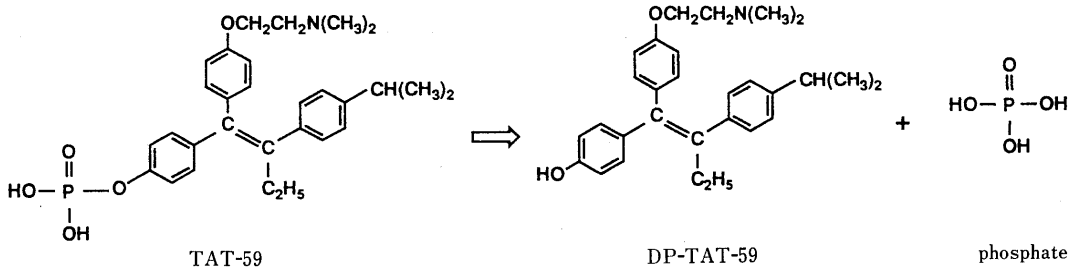

Fig. 1. Chemical Structure of TAT-59, DP-TAT-59 and Phosphate

Seisakusyo Co.) equipped with flat punches of 8.0 mm diameter at 1700 kg·cm^{-2}.

Measurement Tensile Strength; The tensile strength was determined by measuring diameter, thickness and diametrical compression carried out with a Schleuniger-4M (Freund Sangyo Co.). Measurements were performed on five or ten tablets in each instance.

Porosity: The densities of TAT-59 and excipients measured with an Air comparison pycnometer (Toshiba-Beckman Co., Ltd., Model 930) are shown in Table II. The porosity of a tablet was determined by measuring weight, diameter and thickness of the tablet and density of the powder.

Water Content: The Formulated tablet and TAT-59 tablet were crushed to a powder in a mortar, and the powder (0.3 g) was placed in Karl Fisher apparatus (MKA-3p, Kyoto Electric Co., Ltd.).

Amount of TAT-59: The Formulated tablet, TAT-59 tablet, crushed into powder and TAT-59 powder were weighed accurately. To a portion of the powder, equivalent to about 20 mg of TAT-59, were added 45 ml of the mobile phase and 5 ml of the internal standard solution (Butyl *p*-hydroxybenzoate; 0.4 mg·ml^{-1}). The content of TAT-59 was determined by high-performance liquid chromatography (HPLC) (JASCO-800; Japan Spectroscopic Co., Ltd.) equipped with an octodecyl silica (ODS) column (5 μm 150 × 4.6 mm; GL Sciences Co.). The mobile phase consisted of 0.1 M Na_2HPO_4 (pH 6.8), water and acetonitrile (50 : 650 : 300).

Amount of DP-TAT-59: The Formulated tablet, TAT-59 tablet, crushed into powder and TAT-59 powder were weighed accurately. To a portion of the powder, equivalent to about 10 mg of TAT-59, were added 5 ml of a mixture of 0.4 N NaOH and methanol solution (1 : 9). The content of DP-TAT-59 was determined by HPLC. The mobile phase consisted of 0.1 M Na_2HPO_4 (pH 6.8), water and 80% acetonitrile (1 : 99 : 400).

Storage Conditions: Formulated tablet, TAT-59 tablet and TAT-59 powder were kept at 50 °C in exsiccators containing saturated salt solutions to maintain 30, 50, 75 and 85% RH for 60 d. Diphosphorus pentaoxide was used to obtain 0% RH. On a specified day, water content, tensile strength, porosity, and amounts of TAT-59 and DP-TAT-59 were measured. The Formulated tablet was also kept at 25, 40, 50 and 60 °C in exsiccators containing saturated salt solutions to maintain 50% RH for 60 d. On a specified day, the amounts of TAT-59 and DP-TAT-59 were measured.

Results and Discussion

Water Content Figure 2 shows the time courses of water content of Formulated tablet, TAT-59 tablet and TAT-59 powder kept at various RH for 60 d. Original water content was 5.5, 3.6 and 3.4%, respectively. The water content of Formulated tablet kept at 50—85% RH increased by 5—50% and equilibrated in 3 d. The equilibrium value increased with RH. The water content of Formulated tablet kept at 30% RH scarcely changed for 60 d, and that kept at 0% RH decreased. The change in 0% RH was attributed to gradual loss of crystal water of lactose. The water content of TAT-59 tablet and TAT-59 powder kept at 30—85% RH changed little during 60 d, and that at 0% RH became zero at 15 and 3 d, respectively. The water content of TAT-59 tablet was slightly higher than that of TAT-59 powder at 75—85% RH. More water may have been incorporated into TAT-59 tablet than into TAT-59 powder due to capillary action.

TABLE II. Particle Diameter and Density of Powders Used

	TAT-59	Lactose	Microcrystalline cellulose	Hydroxypropyl starch
Particle diameter (μm)	1.6 ±0.01[a]	9.3 ±0.04	4.6 ±0.05	12.9 ±0.09
Density (g·ml^{-1})	1.21±0.006[a]	1.55±0.005	1.56±0.002	1.47±0.002

a) ±S.D., $n=3$.

Tensile Strength Figure 3 shows changes in the tensile strength of Formulated tablet and TAT-59 tablet kept at various RH. Original tensile strength was 17.5 and 30.3 kg·cm^{-2}, respectively. The strength of Formulated tablet kept at 30—85% RH decreased by 18—66% and equilibrated in 3 d. The equilibrium values decreased with increasing RH; that at 0% RH decreased over 60 d. Tensile strength of TAT-59 tablet kept at 50—85% RH decreased by 14—36% and equilibrated in 3 d. That at 30% RH changed little, and at 0% RH increased by 26% and equilibrated in 16 d.

Porosity Changes in the porosity of Formulated tablet and TAT-59 tablet kept at various RH are shown in Fig. 4. The original values were 0.12 and 0.05, respectively. The porosity of the Formulated tablet kept at 30—85% RH increased by 8—91% and equilibrated in 3 d; the equilibrium value increased with RH. The porosity at 0% RH decreased from the beginning to 7 d and gradually increased from 7 to 60 d, while that of the TAT-59 tablet kept at any RH scarcely changed during 60 d.

The equilibrium tensile strength and porosity of the Formulated tablet and TAT-59 tablet kept at 30—85% RH were plotted against equilibrium water content[9] (Fig. 5). The tensile strength of the Formulated tablet and TAT-59 tablet decreased linearly with increasing water content. Porosity of Formulated tablet increased linearly with water content, while that of TAT-59 tablet hardly changed. In the

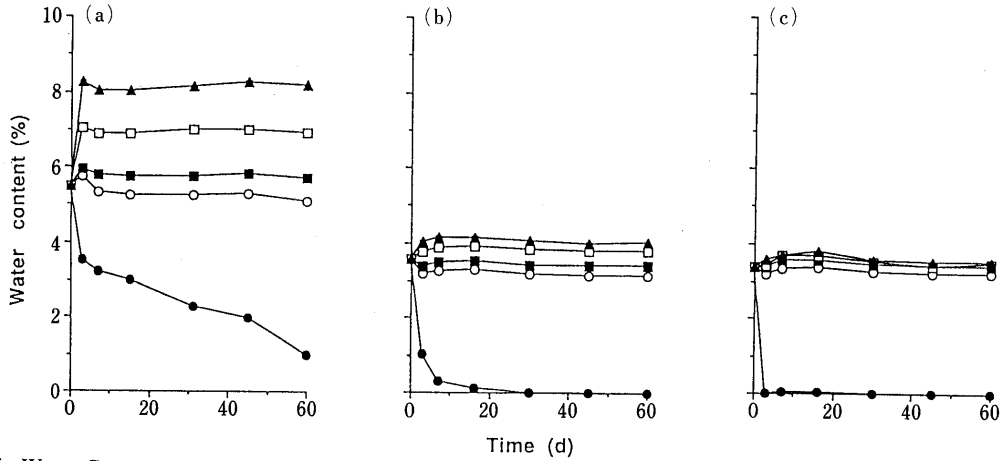

Fig. 2. Changes in Water Content with Time of Formulated Tablet (a), TAT-59 Tablet (b), and TAT-59 Powder (c) at 50 °C under 0 (●), 30 (○), 50 (■), 75, (□), and 85%RH (▲)

Each point represents the mean±S.D.

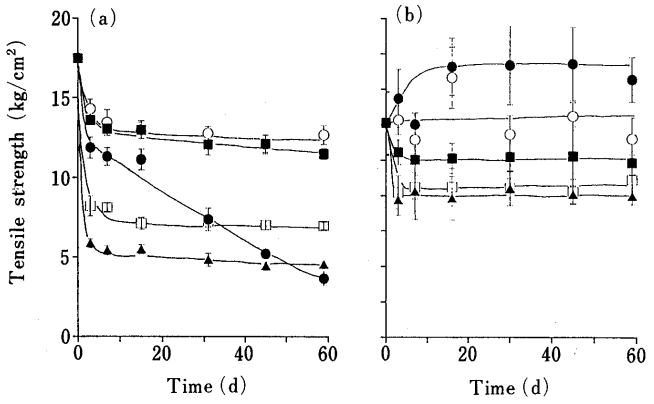

Fig. 3. Changes in Tensile Strength with Time of Formulated Tablet (a) and TAT-59 Tablet (b) at 50 °C under 0 (●), 30 (○), 50 (■), 75 (□), and 85%RH (▲)

Each point represents the mean ± S.D.

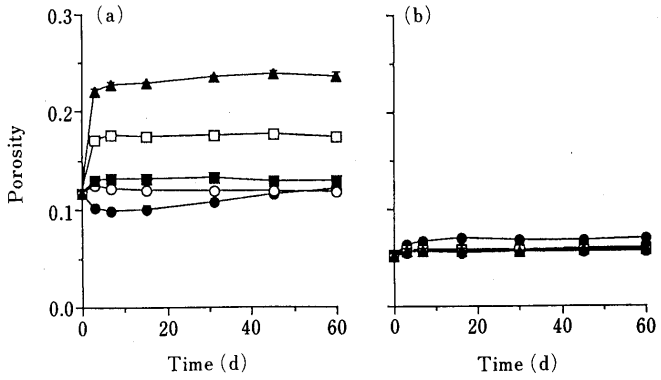

Fig. 4. Changes in Porosity with Time of Formulated Tablet (a) and TAT-59 Tablet (b) at 50 °C under 0 (●), 30 (○), 50 (■), 75 (□), and 85%RH (▲)

Each point represents the mean ± S.D.

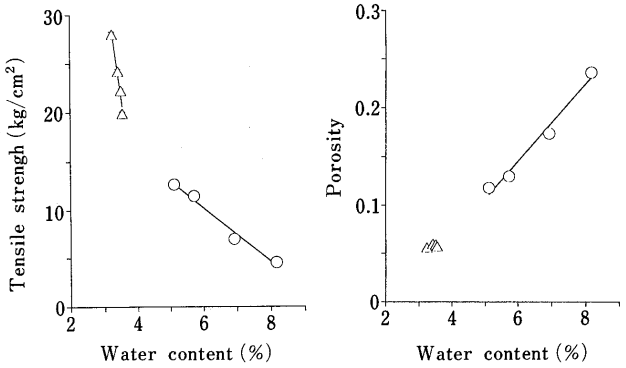

Fig. 5. Relationship between Tensile Strength and Water Content, between Porosity and Water Content of Formulated Tablet (○) and TAT-59 Tablet (△)

Each point represents the mean ± S.D.

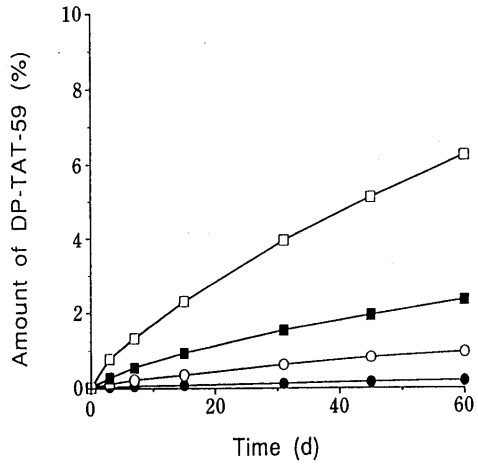

Fig. 6. The Time courses of the Appearance of DP-TAT-59 with Time in Formulated Tablet at 25 (●), 40 (○), 50 (■), and 60 °C (□) under 50%RH

Each point represents the mean ± S.D.

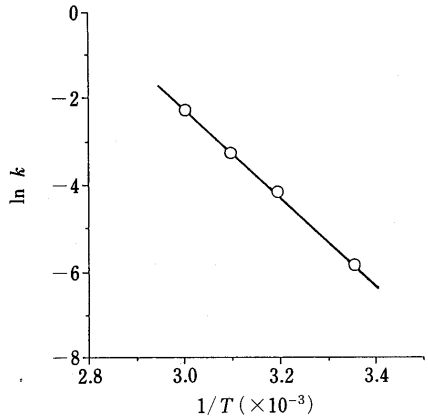

Fig. 7. Arrhenius Plot of the Degradation Rate of TAT-59 in Formulated Tablet

case of Formulated tablet, swelling of microcrystalline cellulose and hydroxypropylstarch by adsorbed water caused the decrease in tensile strength and increase in porosity.[10] The swelling of excipients was considered to equilibrate for about 3 d. In the TAT-59 tablet, it was possible that the small amount of incorporated water was the main factor for decrease in tensile strength, whereas it was considered that the continuous decrease in tensile strength of the Formulated tablet kept at 0% RH was attributable to gradual loss of crystal water of lactose.

Degradation of TAT-59 The amount of DP-TAT-59 in the Formulated tablet kept at 25—60 °C under 50% RH is shown in Fig. 6. Degradation followed apparent zero-order kinetics.

Figure 7 shows Arrhenius plot of the degradation rate of TAT-59 in the Formulated tablet. The plot was linear, and its activation energy was 20.1 kcal·mol^{-1}.

Figure 8 shows the amounts of DP-TAT-59 in the Formulated tablet, TAT-59 tablet and TAT-59 powder kept at various RH. DP-TAT-59 in the Formulated tablet increased by 1—4% for 60 d. The rate increased with RH, and its absolute value was essentially consistent with that of the decrease of TAT-59. DP-TAT-59 in TAT-59 tablet increased by 0.3—0.7%, and that in TAT-59 powder increased by 0.1—0.2% for 60 d.

The equilibrium water content and degradation rate of TAT-59 in Formulated tablet, TAT-59 tablet and TAT-59 powder are compared in Table III. The degradation rate in the Formulated tablet increased with water content, while that in TAT-59 tablet was maximum at a water content of 3.4%. Carstensen *et al.*[5] reported the degradation rate of thiamine hydrochloride in a tablet to be maximum when

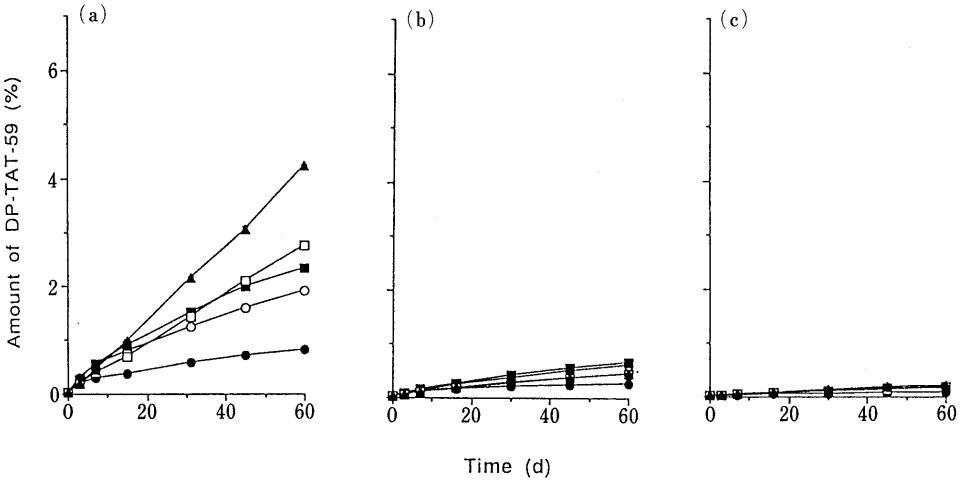

Fig. 8. The Time Courses of the Appearance of DP-TAT-59 with Time in Formulated Tablet (a), TAT-59 Tablet (b) and TAT-59 Powder (c) at 50 °C under 0 (●), 30 (○), 50 (■), 75 (□), and 85%RH (▲)

Each point represents the mean ± S.D.

TABLE III. Equilibrium Water Content and Degradation Rate of TAT-59

RH	Formulated tablet		TAT-59 tablet		TAT-59 powder	
	Water (%)[a]	k (%·d^{-1})	Water (%)	k (%·d^{-1})	Water (%)	k (%·d^{-1})
0	Below 1.0	1.23×10^{-2}	0.0	3.50×10^{-3}	0.0	8.85×10^{-4}
30	5.1	2.98×10^{-2}	3.2	9.34×10^{-3}	3.2	2.50×10^{-3}
50	5.7	3.80×10^{-2}	3.4	1.06×10^{-2}	3.4	2.47×10^{-3}
75	6.9	4.52×10^{-2}	3.8	7.11×10^{-3}	3.5	2.57×10^{-3}
85	8.2	7.02×10^{-2}	4.0	7.22×10^{-3}	3.6	3.26×10^{-3}

a) The equilibrium water content (at 60 d).

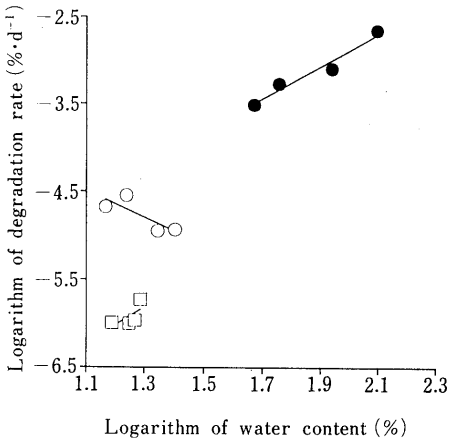

Fig. 9. Relationship between the Degradation Rate and the Water Content in Formulated Tablet (●), TAT-59 Tablet (○), and TAT-59 Powder (□)

water content of the tablet was about 5%. The degradation rate in TAT-59 powder was scarcely influenced by water content.

The effect of water content on the degradation of TAT-59 in all three materials can be analyzed by Carstensen's equation[11,12] as shown below:

$$dC/dt = -k' \cdot C^n \quad (1)$$

$$k' = km^\alpha \quad \text{or} \quad \ln k' = \ln k + \alpha \ln m \quad (2)$$

where C denotes drug concentration, t, time; m, water content; k, rate constant; k', apparent rate constant; n, apparent reaction order; and α interaction order between the drug and water content. For the degradation of TAT-59, n was zero as shown in Fig. 9. The natural logarithm of the degradation rate in the range of 30 to 85% RH is plotted against the natural logarithm of water content in Fig. 10. Since the plot of Formulated Tablet gave a straight line ($\alpha = 1.9$), it was considered that the degradation rate of TAT-59 in Formulated tablet was related to water content in the range of 30 to 85% RH. The plots of TAT-59 tablet and TAT-59 powder are also shown; however, Carstensen's equation may not be applicable to them, because their water content and degradation rate changed little. The degradation in TAT-59 tablet was accelerated compared to TAT-59 powder, and it was speculated that tableting lowered the crystallinity of TAT-59. On the whole, the degradation rate decreased in the following order: Formulated tablet > TAT-59 tablet > TAT-59 powder. The degradation of TAT-59 was accelerated by tableting, and by adding other ingredients.

Conclusions

Changes in tensile strength, porosity and degradation of TAT-59 were influenced mainly by water content of the tablet which, in turn, was affected by the adsorbed moisture of the excipients. Although TAT-59 powder was stable under the experimental conditions, its degradation was accelerated by compression and addition of excipients.

References and Notes

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