Stability and Stabilization Studies of TAK-599 (Ceftaroline Fosamil), a Novel *N*-Phosphono Type Prodrug of Anti-methicillin Resistant *Staphylococcus aureus* Cephalosporin T-91825

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TAK-599 (known as ceftaroline fosamil) is a novel *N*-phosphono type prodrug of a cephalosporin compound, T-91825, that exhibits strong activity against methicillin resistant *Staphylococcus aureus* (MRSA). The stability and stabilization of TAK-599 were investigated by kinetic analysis focused on crystallinity and moisture content. Initially it was planned to develop TAK-599 as an injectable formulation using the amorphous solid powder prepared by lyophilization. However, amorphous of TAK-599 free form was found to be chemically unstable even when stored at 8 °C, and thus development was focused on the crystalline material. After exhaustive screening of crystallization condition, the monoacetic acid solvate was found to yield TAK-599 in a crystalline form. Physicochemical properties were studied to identify the key factors affecting the stabilization of TAK-599 in order to improve long-term stability, and the results indicated that the crystallinity of TAK-599 correlated with stability. Furthermore, moisture content was also identified in our studies as an important factor in stabilizing TAK-599. TAK-599 containing about 3% moisture was found to be the most stable form. It was concluded that both sufficient crystallinity and strict moisture control of TAK-599 were essential to maintain long-term stability at 25 °C.

Key words ceftaroline fosamil; TAK-599; stability; stabilization; crystallinity; kinetic analysis

Generally, most active pharmaceutical ingredients (APIs) used in oral dosage formulations are developed as crystalline forms rather than amorphous materials, since it is easier to control batch quality, impurity levels and maintain stability.[1—3] On the other hand, amorphous APIs typified by lyophilized powders are often preferred to improve solubility in injectable formulations, although the amorphous substance is generally less stable than the crystalline substance.

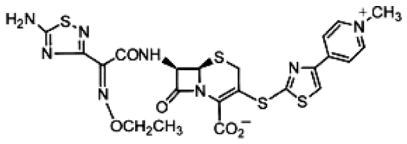
Formulation design based on physicochemical considerations is important for development to maintain the appropriate level of quality and stable supply required for a pharmaceutical. There have been a number of publications describing alterations of physicochemical properties with changes in crystallinity; for example, hygroscopicity,[3—5] crystalline transition,[6] dehydration of crystalline water,[7,8] dissolution rate[9,10] and heat of solution[11,12] studies have all been reported. Although numerous studies regarding stability and stabilization have been reported for cephalosporin antibiotics, which are often physicochemically unstable in the solid state,[13—16] there are not many reports that discuss the relationship between crystallinity and stability.[7,17,18]

TAK-599 (ceftaroline fosamil) [(6*R*,7*R*)-7-({(*Z*)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]-acetyl}amino)-3-{[4-(1-methyl-4-pyridinio)-1,3-thiazol-2-yl]thio}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate acetic acid solvate] is a novel *N*-phosphono type aqueous prodrug of T-91825 that has strong anti-methicillin resistant *Staphylococcus aureus* (MRSA) activity (Fig. 1).[19,20] Since TAK-599 had not been crystallized in a free form in the early research stage, we attempted to develop the compound as an amorphous solid. However amorphous of TAK-599 free form was unstable even when stored cold, and was difficult to develop as a pharmaceutical agent.

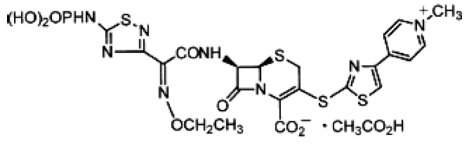
After numerous attempts at crystallization, crystalline TAK-599, acetic acid solvate was crystallized from aqueous acetic acid solution, and the key factors for the stability affecting the stability of TAK-599 were identified by a stability study on TAK-599 crystals. It was found that the crystallinity of TAK-599 and moisture content affected stability in the solid state. In this paper, we report that both sufficient crystallinity and rigorous moisture control are crucial to maintain the quality of TAK-599 in the long term.

Experimental

Materials T-91825 and TAK-599 were synthesized in the Medicinal Chemistry Research Laboratories and the Chemical Development Laboratories at Takeda Pharmaceutical Co., Ltd. Special grade or HPLC grade reagents were obtained from Wako Pure Chemical Industry, Ltd. The acetic acid content of TAK-599, monoacetic acid solvate was confirmed by elemental analysis and the ion chromatography.



T-91825



TAK-599

Fig. 1. Chemical Structure of TAK-599 and T-91825

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Equipment Powder X-ray diffraction was conducted using a RINT 2100 diffractometer (Rigaku Co., Ltd., Japan).

Moisture adsorption and desorption analyses were conducted using an SGA-100 Symmetrical Gravimetric Analyzer (VTI Co., Ltd., U.S.A.).

Water determination (Karl Fischer method) was conducted using an AQ-7 microtitrator (Hiranuma Co., Ltd., Japan).

HPLC measurements were conducted using an L-6200/L-6000 pump, L-4200 UV detector, AS-4000 auto injector (Hitachi Co., Ltd., Japan) and CTO-6A column oven (Shimadzu Co., Ltd., Japan).

Stability in Aqueous Solution About 2 mg of TAK-599 was weighed accurately into a 100 ml volumetric flask and dissolved with Britton-Robinson's buffer solution (pH 3, 4, 5, 6, 7, 9). The sample solution was prepared to make exactly 100 ml with an appropriate Britton-Robinson's buffer solution and stored at 25 °C. Residual percentage was calculated by the ratio of the peak area of TAK-599 from stored injection against that from initial injection after HPLC analysis. Analytical conditions were as follows: detection, UV 254 nm; column, YMC ProC18 75 mm length and 4.6 mm diameter; mobile phase, a mixture of 0.1 mol/l aqueous sodium acetate, 0.1 mol/l acetic acid and acetonitrile (960 : 30 : 130); column temperature, a constant temperature at about 25 °C; flow rate, 1.0 ml/min; and injection volume, 10 μl.

Stability in the Solid State About 20 mg of TAK-599 and amorphous of TAK-599 free form was weighed accurately into a colorless glass vial in a dry box controlled 5 to 10% RH by a dry nitrogen gas flow. The vial was stoppered with a laminate rubber top and crimped with an aluminum cap.

Sample vials of amorphous of TAK-599 free form were stored at −20 °C (MDF-U536D, Sanyo Co., Ltd., Japan), 8 °C (MIR-551, Sanyo Co., Ltd., Japan), 25 °C and 40 °C (LH21-15M, Nagano Science Co., Ltd., Japan). Those of TAK-599 were stored at 40 °C, 50 °C and 60 °C (LH21-15M, Nagano Science Co., Ltd., Japan).

After storage, a sample was dissolved in mobile phase A and transferred to a 25 ml volumetric flask. The sample solution was prepared to make exactly 25 ml with mobile phase A. The sample solution and the standard solution prepared with a frozen storage sample were injected into the HPLC instrument. Residual percentage was calculated by the ratio of the peak area of TAK-599 from the sample solution against that from the standard solution. Analytical conditions were as follows; detection, UV 254 nm; column, YMC ProC18 150 mm length and 4.6 mm diameter; mobile phase A, a mixture of 0.1 mol/l aqueous ammonium acetate and acetonitrile (960 : 65); mobile phase B, a mixture of 0.1 mol/l aqueous ammonium acetate and acetonitrile (960 : 4610); gradient program, mobile phase B from 0 to 5% for 0 to 20 min, B from 5 to 20% for 20 to 40 min, B 20 to 40% for 40 to 50 min; column temperature, a constant temperature at about 25 °C; flow rate, 1.0 ml/min; and injection volume, 10 μl.

Powder X-Ray Diffractometry (XRD) About 10 mg of sample was loaded into a non-reflective holder made from a single crystal of silicon. The X-ray source was Cu$K\alpha$ (λ=1.5418 Å) and the diffraction beam was monochromated by a bent-graphite monochromator. Other conditions were as follows; voltage, 40 kV; current, 50 mA; scatter and receiving slits, 0.45 mm; scanning speed, 6°/min; diffraction angle (2θ), 3° to 40°. The crystallinity of each sample was calculated by Hermans method.[21] The procedure is described as follows: 1) calculate all peak areas from the XRD pattern of the sample; 2) subtract background area from the area of 1) by the blank analysis; 3) subtract the halo pattern derived from amorphous in the sample from the area of 2); 4) calculate the crystallinity of the sample, [area of 3)]/[area of 2)]×100.

Moisture-controlled experiments were conducted with a HUM-1 humidity control system (Rigaku Co. Ltd., Japan).

Water Vapor Sorption Analysis The moisture sorption measurement cycles were started at 5% relative humidity (RH) and increased in 5% steps up to 95% RH and back to 5% RH. The equilibrium condition for each step was set to a weight constancy of ±0.01% over 180 min. The temperature was 25±0.1 °C.

Results and Discussion

Physicochemical Properties of TAK-599 Solubility and stability in aqueous solution were studied to investigate the basic physicochemical properties of TAK-599. TAK-599 was greater than fifty-fold more soluble than T-91825 at pH 7 (Table 1).

TAK-599 decomposed in aqueous solutions under first-order kinetics, and it was found to be most stable at pH 7 (Fig. 2). The residual percentage in pH 7 buffer solution at 25 °C for 24 h was more than 95%, which was considered sufficient stability for an injectable drug. The main degradation product at pH 7 was T-91825.

Table 1. Solubility of TAK-599 and T-91825 at 25 °C

	Solubility (mg/ml)[a]
T-91825	2.3
TAK-599	>100

a) 2 mol/l phosphate buffer solution (pH 7.0).

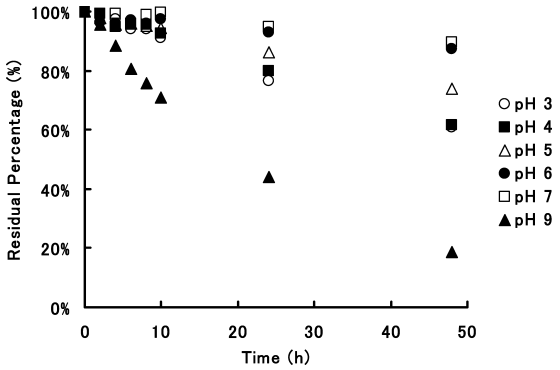

Fig. 2. Stability of TAK-599 in Aqueous Buffer Solutions at 25 °C

Table 2. Stability of Amorphous of TAK-599 Free Form Stored at Various Temperatures

Storage period (month)	Residual percentage			
	−20 °C	8 °C	25 °C	40 °C
0.5	101.6	98.1	92.9	81.7
1	101.1	84.4	87.0	72.6
2	101.5	76.0	49.5	43.1

Stability of Amorphous TAK-599 The stability data for amorphous of TAK-599 free form prepared by lyophilization is shown in Table 2. Amorphous of TAK-599 free form found to be unstable, and the residual percentage of TAK-599 stored at 8 °C for 4 weeks was less than 90%. The main degradation product was T-91825, which is the same as that found in aqueous solution. Amorphous of TAK-599 free form was only stable below −20 °C, and therefore, it was difficult to develop amorphous of TAK-599 free form as a pharmaceutical with sufficient quality.

Some methods have been reported for the stabilization of injectable formulations such as chemical interaction with additives[13] and crystallization of API.[22] Thus stabilization studies were conducted in order to improve the stability of amorphous of TAK-599 free form. However, our results indicated that the addition of inorganic salts, sugars and amino acids as reported by Ashizawa *et al.*,[13] was ineffective at stabilizing TAK-599, and it was therefore necessary to investigate stabilization through crystallization.

Stability of TAK-599 Monoacetic Acid Solvate and a Correlation Study between Crystallinity and Stability A crystalline mono acetic acid solvate, TAK-599 was discovered by the medicinal chemists after numerous crystallization

Table 3. Stability of TAK-599 for Batches with Varying Crystallinity at 40 °C, 50 °C and 60 °C

Crystallinity (%)	Moisture content (%)	Storage period (month)	Residual percentage (%)		
			40 °C	50 °C	60 °C
70	2.8	0	100	100	100
		0.5	96.8	96.4	92.8
		1	96.6	95.1	92.3
		2	96.6	94.8	90.7
		4	96.0	95.0	89.5
64	2.6	0	100	100	100
		0.5	96.1	95.2	90.3
		1	94.9	94.3	89.3
		2	94.2	91.1	87.4
		4	93.8	91.2	85.1
59	2.8	0	100	100	100
		0.5	94.7	94.7	90.7
		1	93.7	92.9	89.5
		2	92.3	91.0	85.2
		4	90.5	88.0	84.3
49	2.9	0	100	100	100
		0.5	95.1	93.1	91.5
		1	91.7	91.3	85.4
		2	90.1	87.4	84.3
		4	88.9	85.6	81.7

efforts. Drug substances possessing a range of crystallinities were obtained after exhaustive crystallization trials. Four batches of TAK-599 having different crystallinity (crystallinity values: 70%, 64%, 59%, 49%) were synthesized and their relative stability was studied. The test results are shown in Table 3. All of the crystalline batches were more stable than the amorphous material, and in addition the results showed that the stability was remarkably improved with increasing crystallinity of the material. It was confirmed that the crystallinities of stored samples were constant over time and there was no change in the acetic acid content.

The degradation time course is shown in Fig. 3. Initially, a rapid degradation is found at the early stages of storage, which is followed by a later gradual degradation, which occurs upon prolonged storage.

Generally, degradation reactions in the solid state proceed non-uniformly and the reaction state is complicated. Many theoretical models have been proposed to describe solid state reactions, of which the Jander equation, a three-dimensional diffusion model[23]; the Avrami equation, a three-dimensional nucleation growth model[24]; and the Mampel equation, a three-dimensional phase boundary model[25] are the most well-known.

The stability results for TAK-599 were analyzed using these equations, however, no equation showed a significant correlation. The main cause for poor correlation was the remarkable degradation pattern of TAK-599, in particular, the abrupt degradation at the early stages of storage. It was speculated that the degradation mechanism of TAK-599 was too complicated to solve by preexisting equations and the reaction rate constitutively changed during storage.

In order to investigate the complicated mode of action of the solid-state reaction, analysis using empirical formulae was necessary to solve the kinetics. The Weibull equation, which is one of the representative set of empirical formulae used to elucidate the correlation between storage period and degradation ratio was employed for kinetic analysis.[26,27] The

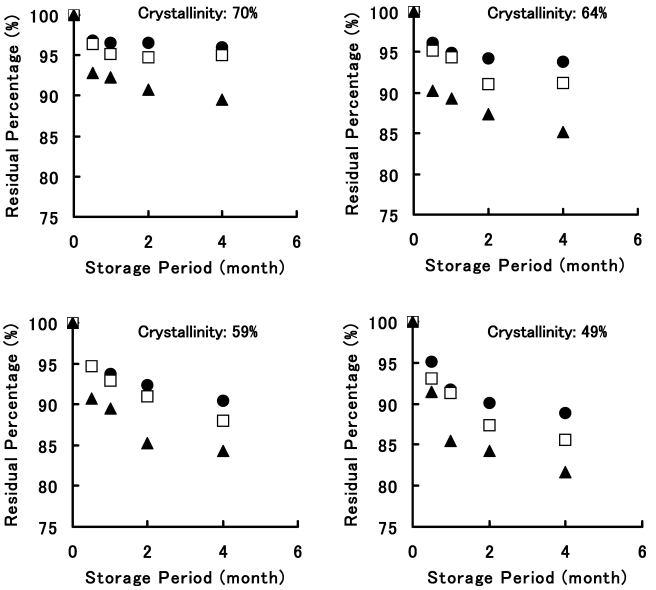

Fig. 3. Decomposition Curves of TAK-599 for Batches with Varying Crystallinity

● 40 °C, □ 50 °C, ▲ 60 °C.

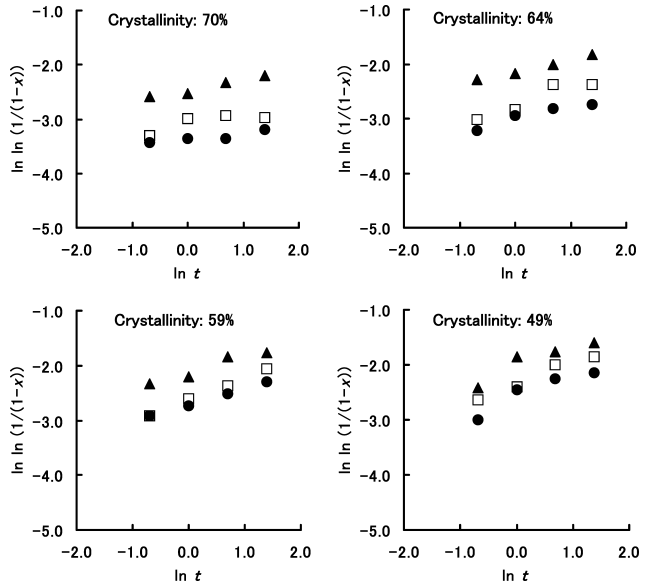

Fig. 4. Degradation Ratio of TAK-599 Stability for Batches with Varying Crystallinity

● 40 °C, □ 50 °C, ▲ 60 °C.

equation is described below:

$$\ln\ln(1/(1-x)) = \ln k + m \cdot \ln t$$

where x is degradation ratio, t is time, and m and k are parameters.

The test results of TAK-599 were analyzed by the Weibull equation, and the relationship between $\ln t$ and $\ln\ln(1/(1-x))$ are plotted in Fig. 4 and the calculated values of m and $\ln k$ are shown in Table 4.

Furthermore, $1/T$ and $1/m \cdot \ln k$ were plotted using the m and $\ln k$ values shown in Table 4. A good linear correlation was observed for each crystallinity (Fig. 5).

From the slope of each linear equation, $1/m \cdot \ln k$ at 25 °C,

Table 4. Parameters m and $\ln k$ Estimated by Weibull Plots of Stability of TAK-599 for Batches with Varying Crystallinity

	Crystallinity							
	70%		64%		59%		49%	
	m	$\ln k$	m	$\ln k$	m	$\ln k$	m	$\ln k$
40 °C	0.0984	−3.3722	0.2249	−3.0131	0.2923	−2.7191	0.3950	−2.5963
50 °C	0.1541	−3.1027	0.3634	−2.7627	0.4239	−2.6203	0.3928	−2.3613
60 °C	0.1995	−2.4801	0.2234	−2.1500	0.2951	−2.1334	0.3672	−2.0217

Table 5. Estimated Kinetic Parameters for the Stability of TAK-599 for Batches with Varying Crystallinity

	Crystallinity			
	70%	64%	59%	49%
$1/m \cdot \ln k$ at 25 °C	−51.714	−15.383	−10.413	−7.427
Activation energy (kJ/mol)[27]	949	167	92	45
Estimated residual percentage after storage at 25 °C for 36 months[27]	99.9%	96.0%	90.5%	79.6%

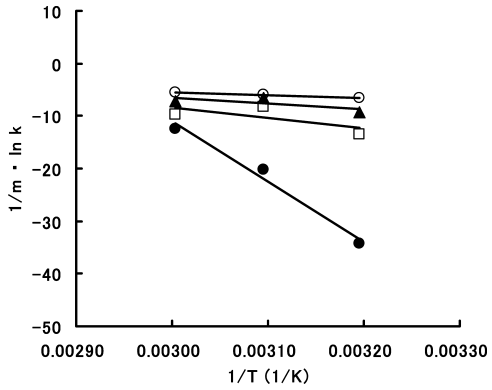

Fig. 5. Temperature Dependency of $1/m \cdot \ln k$ for the Degradation of TAK-599 for Batches with Varying Crystallinity

Crystallinity: ●, 70%; □, 64%; ▲, 59%; ○, 49%.

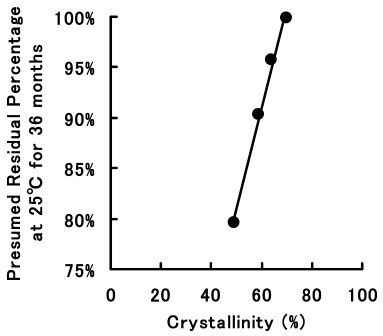

Fig. 6. Correlation between Crystallinity of TAK-599 and Estimated Residual Percentage at 25 °C for 36 months

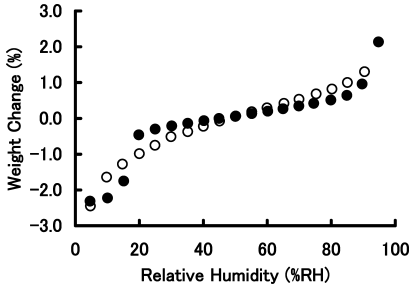

Fig. 7. Moisture Adsorption and Desorption Isotherms of TAK-599 at 25 °C

● adsorption, ○ desorption.

the activation energy and presumed residual percentage at 25 °C after 36 months were calculated (Table 5). Both the $1/m \cdot \ln k$ value and especially the activation energy were greatly altered by increasing crystallinity. The activation energies of lower crystallinity batches were relatively low, and the degradation reaction progressed with little temperature-dependency. These results suggested that it would be extremely difficult to maintain sufficient quality for lower crystallinity batches and that crystallinity is the one of the key parameters that determines the solid-state stability of TAK-599.

The correlation between crystallinity and estimated residual percentage at 25 °C after 36 months is shown in Fig. 6. If the criterion for residual percentage at 25 °C for 36 months was set at greater than 95%, the lowest level of crystallinity acceptable was calculated to be about 60 to 65% from this approximated equation.

Analysis of Influence of Moisture Content on Stability Stabilization of TAK-599 by crystallization was described in the previous section. However, stability is often affected by moisture content and in particular degradation reactions are reported to be accelerated by the destruction of the crystalline structures of hydrates.[16,28]

Moisture adsorption and desorption isotherms of TAK-599 at 25 °C are shown in Fig. 7. This compound showed multilayer adsorptive hygroscopicity. The moisture contents of typical TAK-599 batches were around 3%, which is nearly equivalent to that of the monohydrate. X-ray powder diffraction patterns were measured under dry nitrogen conditions to analyze the influence of moisture on the crystalline form (Fig. 8), and it was found that the diffraction pattern changed after only 10 min drying, giving a new pattern which was basically similar to that of the intact form. Moisture readily dissociated from TAK-599 under dry conditions and the hydrate

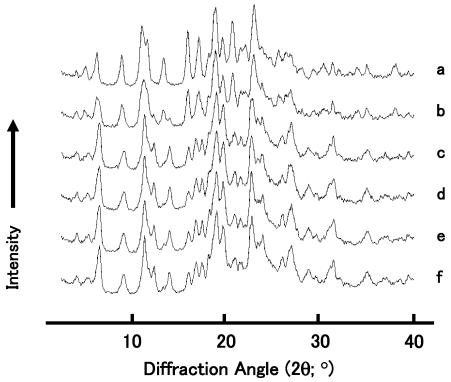

Fig. 8. Crystalline Changes of TAK-599 Stored under Dry Conditions
(a) Intact phase (hydrate), (b) 5 min, (c) 10 min, (d) 30 min, (e) 1 h, (f) 2 h.

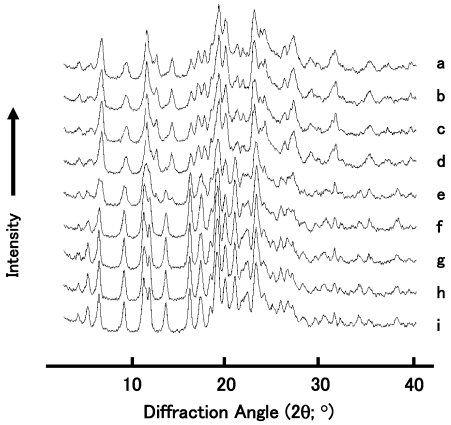

Fig. 9. Crystalline Changes of TAK-599 Anhydrate Exposed at 50% RH
(a) Intact phase (anhydrate), (b) adjusted to 50% RH, (c) 5 min, (d) 10 min, (e) 20 min, (f) 30 min, (g) 1 h, (i) 2 h.

was transformed to an anhydrate, as shown by the decease in the moisture content to 0.2% after 30 min drying as measured by Karl Fischer titrimetry. Anhydrate crystal was also reconstructed to hydrate easily, as demonstrated by the X-ray powder diffraction pattern of the hydrate being reconstructed from the anhydrate stored under 50% RH for 30 min (Fig. 9).

The hydration system of TAK-599 was presumed to be a clathrate hydrate, since the X-ray powder diffraction pattern of the anhydrate was very similar to that of the hydrate. In addition, a non-stoichiometric hydrate formed and hydration water showed readily reversible absorption and desorption behavior.[29)]

The crystalline form of TAK-599 was transformed easily by changes in humidity. Although TAK-599 exists as a hydrate under the ambient conditions, the water of hydration is readily removed under drying conditions. Since the drying process is an essential part of the manufacturing process of drug substances, there was a concern about varying moisture content and crystalline form during the manufacturing process of TAK-599.

The stability of TAK-599 having various moisture contents was studied at 40 °C (Table 6). Hydrate containing approximately one molar equivalent of water (moisture content: 2.8%) was slightly more stable than anhydrate (moisture content: 0.3%) or drug substance containing more than approximately one equivalent of water. It is presumed that hydrolysis is promoted by additional water.

Table 6. Stability at 40 °C of TAK-599 Batches with Varying Moisture Content

Storage period (month)	Residual percentage (%)			
	Moisture content			
	4.7%	4.1%	2.8%	0.3%
0	100	100	100	100
1	94.6	95.8	96.6	96.5
2	93.0	94.3	96.6	96.1
4	88.2	93.4	96.0	95.5

The crystallinity of tested samples was controlled at approximately 70%.

In addition to maintaining high crystallinity, it is important to control the moisture content of TAK-599 to retain sufficient quality. Adequate humidity control is necessary to maintain suitable moisture content.

Conclusion

Stabilization of TAK-599 was investigated to improve long-term stability under the ordinary conditions. We established that the crystallinity of TAK-599 was the key factor for maintaining stability, and significant correlation was found between crystallinity and stability. Furthermore, moisture content also contributed to the stability of TAK-599, and the optimal moisture content was around 3%, which was most stable stored at 40 °C.

This study therefore demonstrated that improved crystallinity and adequate moisture control hold the key to stabilizing TAK-599, and that drug substance with the appropriate physicochemical properties should be stable for long-term storage under general conditions.

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