

The Effects of Impurities on Crystallization of Polymorphs of a Drug Substance AE1-923

Masaki OKAMOTO^{1,2}, Masaya HAMANO²,
Koichi IGARASHI¹ and Hiroshi OOSHIMA¹

¹Department of Applied and Bioapplied Chemistry,
Graduate School of Engineering, Osaka City University,
3-138, Sugimoto 3, Sumiyoshi-ku, Osaka 558-8585, Japan

²Fukui Research Institute, Ono Pharmaceutical Co., Ltd.,
5-2, Yamagishi Technoport Mikuni-cho 1, Sakai-gun,
Fukui 913-8538, Japan

Keywords: Solvent-Mediated Transformation, Crystal Polymorphs, Drug Substance, Impurity, Inhibition of Transformation

The effects of seven kinds of impurities on the solvent-mediated transformation of crystal polymorphs of a drug substance AE1-923 were investigated. AE1-923 was developed for an indication of pollakiuria and pain. It has three polymorphs, namely the unstable A-form, the metastable B-form and the stable C-form. The impurities tested were the starting compounds, the reaction reagents and the intermediates in the synthesis of AE1-923. One of the impurities, an intermediate AE1-923ME (methylester of AE1-923), inhibited the solvent-mediated polymorph transformation of the B-form to the C-form, although the transformation of the A-form to the B-form was not inhibited. The other impurities had no effect on the two steps of polymorph transformation. The inhibitory effect of AE1-923ME that was evaluated by the overall transformation rate constant k_c exponentially increased with an increase in the concentration of AE1-923ME. AE1-923ME of 0.5 wt% completely suppressed the nucleation of the stable C-form crystals. However, crystal growth of the C-form was not inhibited.

Introduction

In the manufacturing of pharmaceuticals, polymorphism of crystals must be strictly controlled, because it significantly influences the bioavailability of a drug (Yokoyama *et al.*, 1981; Audran *et al.*, 1988). Impurity is one of the important factors in control of crystal polymorphism. Polymorphism is often affected by a trace amount of impurities (Davey, 1997; Domopoulou 1998). Many drug substances are synthesized through many reactions. It means that many kinds of chemicals, namely raw materials, intermediates, by-products, etc., may be remained in the solution of final product as a trace amount of impurities. Therefore, it is important to understand the effects of the impurities on appearance of crystal polymorphs. However, there have not been so many reports with respect to the effect of impurities on the crystallization of polymorphs of drug substances (Kuroda *et al.*, 1979; Kato *et al.*, 1981).

The aims of this report are to show and to discuss an example that an intermediate in the synthesis of a drug substance inhibited the solvent-mediated transformation of crystal polymorphs of a final product. In

the present study, a drug substance AE1-923 (4-[[2-[N-(5-Methylfuran-2-sulfonyl)-N-isopropylamino]-5-(trifluoro-methyl) phenoxy] methyl] benzoic acid) was crystallized. AE1-923 was developed for an indication of pollakiuria and pain. It has three crystal polymorphs in a mixed solvent of ethanol and water, namely the unstable A-form, the metastable B-form and the stable C-form (Okamoto *et al.*, 2004). The A-form transforms to the C-form through the B-form and the transformation was promoted with an increase in the crystallization temperature and the ethanol ratio of an ethanol–water mixed solvent (Okamoto *et al.*, 2004).

1. Experimental

1.1 Materials and identification of polymorphs

AE1-923 and its synthetic intermediates shown in **Figure 1** were provided by Ono Pharmaceutical Co., Ltd. The chemical purity of AE1-923 assayed by HPLC was higher than 99.7% and no impurity was contained at the level exceeding 0.1%. The chemical purities of other substances relating to the synthesis of AE1-923, which were used as impurities, were higher than 97%.

The other chemicals used were of the reagent grade and purchased from Wako Pure Chemical Industries, Ltd. Water used was of the manufacturing-grade guaranteed in the drug manufacturing specification. It

Received on January 7, 2004. Correspondence concerning this article should be addressed to H. Ooshima (E-mail address: ooshima@bioa.eng.osaka-cu.ac.jp).

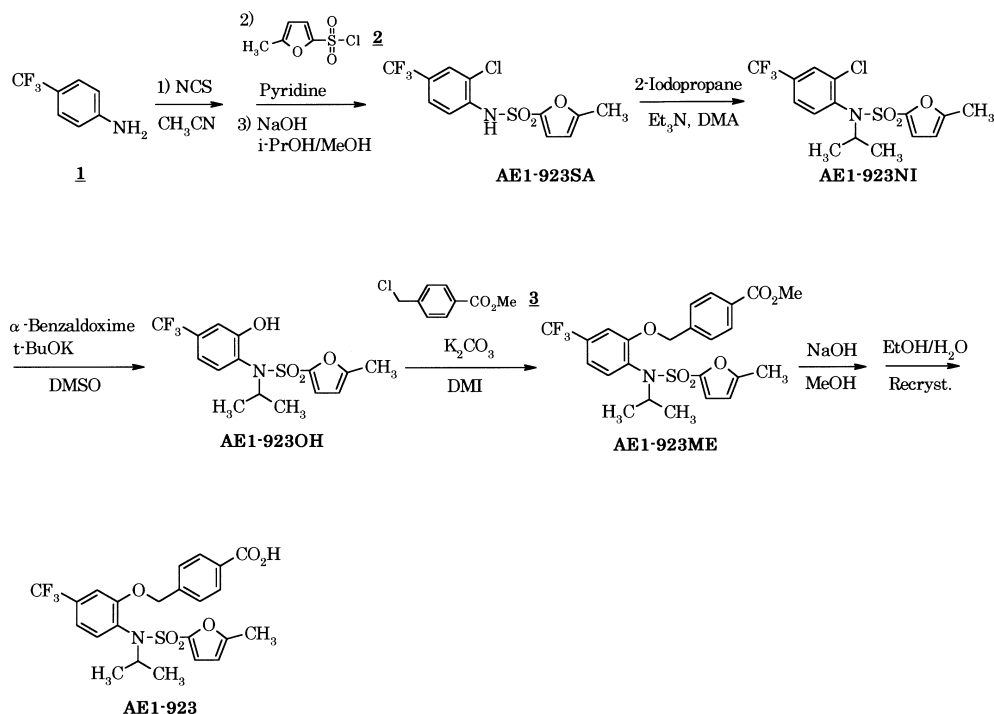


Fig. 1 Synthesis of AE1-923

was fully compliant with the drug manufacturing standard and its quality was guaranteed. An ethanol–water mixed solvent was prepared. In this paper, a mixed solvent containing *N* volume-% ethanol is expressed as *N*%-E solvent, for example 60%-E solvent.

Polymorphs were identified by IR spectroscopy (*in situ*-FTIR Model ReactIR 1000, ASI Applied systems Inc.). **Figure 2** presents the characteristic IR absorption spectrum from 850 to 900 cm^{-1} of each crystal polymorph of AE1-923. The different polymorphs could be distinguished from their peak intensities, namely at 880, 870, and 860 cm^{-1} for the A-, the C-, and the B-forms, respectively. IR spectroscopy was also used to determine the composition of the polymorphs, where the limit of detection of polymorph was approximately 5%.

1.2 Solubility

Using the *in situ*-FTIR system (Okamoto *et al.*, 2004), solubility of three kinds of polymorphic crystals of AE1-923, namely the A-, B-, and C-form crystals were measured in a 60%-E solvent. The solubility of crystals of an intermediate compound AE1-923ME (methylester of AE1-923) was also measured in the same condition.

1.3 Crystallization and effects of impurities on the solvent-mediated transformation of the A-form to the C-form

The poor solvent crystallization of AE1-923 was carried out in the presence and absence of impurities. A jacketed cylindrical glass vessel of 500 mL with an agitator was used as a crystallizer (Okamoto *et al.*,

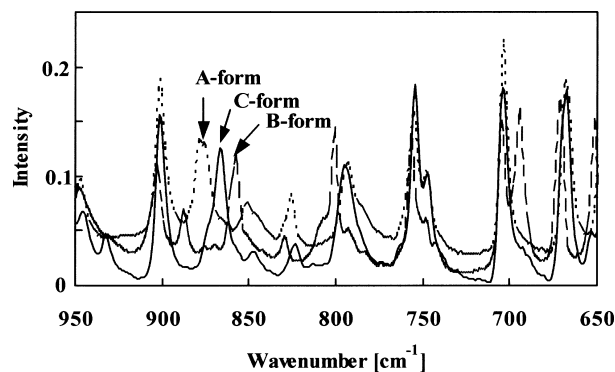


Fig. 2 IR spectra of three polymorphs of AE1-923 crystals

2004). The crystallization was separated into three steps, namely the first step was the exclusive formation of the A-form crystals not containing the B-form and the C-form crystals, the second step was the transformation of the A-form to the B-form, and the third step was the transformation of the B-form to the C-form.

First, the unstable A-form crystals were exclusively precipitated as follows (Okamoto *et al.*, 2004). 105 mL of 50%-E solvent was placed in the crystallizer at 0°C. 15 g of AE1-923 was separately dissolved in 75 mL of ethanol at 35°C. The whole solution was added to the solvent in the crystallizer under stirring at 300 rpm. The precipitation of the A-form crystals was continued for 30 min, where the temperature of

coolant circulating through the jacket was controlled at 0°C and the working concentration of ethanol was 70%. The A-form crystals did not transform to the B-form during the precipitation. We separately confirmed no transformation to the B-form within at least 24 h. No transformation is due to a low crystallization temperature (Okamoto *et al.*, 2004). Second, the solvent-mediated transformation of the A-form to the B-form was started as follows. The ethanol concentration of slurry of the A-form crystals prepared above was decreased to prevent the direct and uncontrolled rapid transformation to the stable C-form. Namely, 7.5 mL of ethanol and 37.5 mL of water were added to the slurry for adjusting the ethanol concentration to 60%. Then the temperature of the slurry was raised to 45°C. Part of the slurry was pipetted at regular intervals and filtered with a 0.45 μm membrane filter. The crystals recovered were dried at 40°C under reduced pressure and their crystal polymorphs were analyzed by FTIR. Third, the solvent-mediated transformation of the B-form to the C-form was started by raising the slurry temperature of the B-form crystals from 45 to 60°C.

The effects of impurities on the solvent-mediated transformation of AE1-923 crystals were examined as follows. Seven kinds of impurities shown in Figure 1 were used, namely the starting material (1), the reaction reagents (2, 3) and the reaction intermediates, AE1-923SA, AE1-923NI, AE1-923OH, AE1-923ME. An impurity was added to the AE1-923 solution before mixing with 105 mL of 50%-E solvent placed in the crystallizer. The impurity concentration was 0.5 wt% on a basis of the weight of AE1-923 used. Precipitation of the A-form crystals and the transformation of the A-form to the B-form and the transformation of the B-form to the C-form were evaluated.

1.4 The effect of AE1-923ME on the solvent-mediated transformation of the B-form to the C-form

Since AE1-923ME inhibited the solvent-mediated transformation of the B-form to the C-form as described later, several experiments were conducted to understand which processes were inhibited by AE1-923ME among three process of the transformation, namely dissolution of the B-form crystals, nucleation and crystal growth of the C-form crystals.

First, the dissolution rate of the B-form crystals was compared between in the absence and the presence of AE1-923ME. A 225 mL of 60%-E solvent was placed in a glass vessel of 500 mL and raised to 60°C. Then 15 g of the B-form crystals of AE1-923 was added under stirring at 300 rpm. The change in the concentration of AE1-923 was continuously measured with an *in situ*-FTIR system. When dissolution rate was measured in the presence of AE1-923ME, 75 mg (0.5 wt%) of AE1-923ME was dissolved in the solvent.

Second, in order to understand the effect of AE1-923ME on nucleation and crystal growth of the C-form

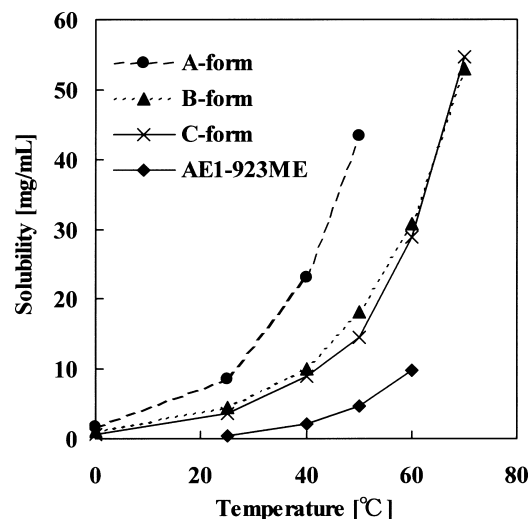


Fig. 3 Solubility curves of AE1-923 crystals and AE1-923ME in 60%-E solvent

crystals, the effect of the timing of impurity addition on the solvent-mediated transformation was investigated. 0.5 wt% of AE1-923ME was added to the slurry of the B-form crystals before or after starting the transformation of the B-form to the C-form.

Third, the effect of AE1-923ME on the growth of the C-form crystals was investigated by using seed crystals of the C-form in the presence of AE1-923ME. The C-form seed crystals of 24 wt% against the potential amount of precipitation of AE1-923 were added to the slurry of the B-form pre-incubated at 60°C for 2 h in the presence of 0.5% AE1-923ME. Two kinds of seed crystals differing in size were used, namely 16 and 1.4 μm in average particle diameter. The latter was prepared by grinding the former. The particle size was determined by the laser reflection method (FBRM, Lasentec Co. Ltd.). Other crystallization operation was the same as that mentioned above.

2. Results and Discussion

2.1 Identification of the impurity affecting the solvent-mediated transformation of the A-form of AE1-923 crystals to the C-form

AE1-923 consists of a benzoic derivative containing trifluoromethylphenyl group and a methylfuran-sulfonyl group, whose synthesis scheme is shown in Figure 1. Crude product was obtained by crystallization after hydrolysis of AE1-923ME. All intermediates of AE1-923 were crystalline solids.

As described above, AE1-923 has three crystal polymorphs in a ethanol–water mixed solvent, namely the unstable A-form, the metastable B-form and the stable C-form. The solubility of each crystal polymorph in 60%-E solvent is presented in Figure 3. Each value was an average of three experimental data that agreed

Table 1 The effects of impurities on the solvent-mediated transformation of AE1-923ME crystals

Impurities (0.5 wt%)*	Effect on the precipitation**	Effect on the transformation**	
	A-form	A-form → B-form	B-form → C-form
Compound 1	×	×	×
Compound 2	×	×	×
Compound 3	×	×	×
AE1-923SA	×	×	×
AE1-923NI	×	×	×
AE1-923OH	×	×	×
AE1-923ME	×	×	○

*the ratio of impurities to AE1-923

**×, not affected; ○, inhibited

within a 2% error. IR analysis confirmed that the transformation of crystal polymorphs did not proceed during the measurement of solubility. The solubility of the unstable A-form was two or three times larger than that of the other two polymorphs. The solubility of the B-form is close to that of the C-form. The solubility curves of the B- and C-forms showed an enantiotropic system. Namely the solubility curves of the two forms crossed at a certain temperature near 65°C.

When purified AE1-923 was used in the poor solvent crystallization, the reproducible experimental data were always obtained. For example, in the crystallization at 40°C in 60%-E solvent, the consecutive transformation of the A-form to the C-form via the B-form was always completed within 3 h (Okamoto *et al.*, 2004). However, when crude AE1-923 was used, the crystallization was not reproducible. Namely, the recovery of each polymorph was different case by case. For example, when the crystallization was carried out in 50%-E solvent at 40°C for 5 h, the B-form ratio of product crystals changed between 0.1 and 1.0 (data also not shown). The B-form ratio of 1.0 means that the solvent-mediated transformation of the B-form to the C-form did not progress. This result suggested that certain impurities inhibited the solvent-mediated transformation of the B-form to the C-form.

We attempted to identify the impurities affecting the solvent-mediated transformation of AE1-923 polymorphs. The impurities should be the chemicals included in the synthesis process shown in Figure 1. The substances examined as impurity were 7 kinds of chemicals listed in **Table 1**. Their effects on the consecutive solvent-mediated transformation of the A-form to the C-form via the B-form were examined. First, as mentioned in the experimental section, the A-form crystals were precipitated by poor solvent operation in the presence of impurities and then the consecutive transformation to the C-form crystals was started by add-

ing ethanol to the slurry of the A-form crystals and raising temperature to 45°C. The experimental results obtained for 7 kinds of impurities were summarized in Table 1. All impurities showed no effect on the precipitation of the A-form crystals as long as it was evaluated from the amount of the A-form crystals recovered. Namely, in all cases, the whole amount of A-form crystals potentially expected from the solubility was recovered after 30 min-crystallization. The transformation of the A-form to the B-form also was not affected by any impurity examined. Namely, in all cases, the A-form crystals completely transformed to the B-form crystals through 30 min-incubation of the A-form crystals at 45°C in 60%-E solvent. The transformation of the B-form to the C-form was inhibited by an intermediate AE1-923ME as shown in Table 1 and **Figure 4**. AE1-923ME is a reaction precursor of AE1-923. 0.5 wt% of AE1-923ME completely disturbed the transformation of the B-form to the C-form. This result suggested that the fluctuation of the B/C polymorph ratio obtained in the crystallization of crude AE1-923 was caused by a trace of AE1-923ME remained in the crystallization solution as an impurity. Indeed, as Figure 2 also shows, the solubility of AE1-923ME is high enough to contaminate a crystallization solution.

2.2 The effect of the AE1-923ME concentration and temperature on the solvent-mediated transformation of the B-form to the C-form

The effect of the concentration of AE1-923ME on its inhibitory effect in the transformation of the B-form to the C-form was investigated at 60°C using 60%-E solvent. Since the transformation of the A-form to the B-form was not influenced by AE1-923ME at all as mentioned above, the transformation was started from the A-form crystals to fix the starting condition of the transformation of the B-form to the C-form as described in the experimental section. The concentration of AE1-923ME was changed from 0.05 to 0.5 wt% and the

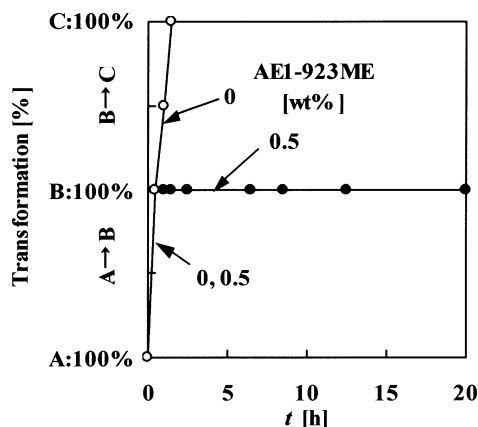


Fig. 4 The effects of AE1-923ME on the transformation of the A-form to the B-form and that of the B-form to the C-form in 60%-E solvent at 45°C

inhibitory effect was evaluated by a time-dependency of the weight ratio of the C-form crystals, X_C , defined by Eq. (1),

$$X_C = W_C / (W_B + W_C) \quad (1)$$

where W_B and W_C are the weights of the B-form crystals and the C-form crystals contained in product crystals, respectively. In Eq. (1), the weight of the A-form crystals is not included, because all the A-form crystals transformed to the B-form crystals.

Figure 5(a) presents changes in X_C . Usually, the transformation time t is originated at the beginning of crystallization of the metastable polymorph, but in the present work the transformation time “zero” was set at the time when the temperature began to increase to 60°C to start the transformation as mentioned in experimental section. Figure 5(a) shows that the transformation started without any waiting time and that the larger the concentration of AE1-923ME, the more strongly the transformation was inhibited, while the transformation was completed within 30 min in the absence of AE1-923ME. AE1-923ME of 0.5 wt% completely inhibited the transformation.

Quantitative evaluation for the solvent mediated transformation of the B-form to the C-form was attempted. A solvent-mediated transformation consists of three processes: i) the nucleation of the stable form; ii) the crystal growth of the stable form; iii) the dissolution of the metastable form. When the crystal growth of the stable form is a rate-determining step and the growth rate is proportional to the crystal surface area, changes in the weight ratio of the C-form crystals, X_C , can be expressed by,

$$dX_C/dt = kX_C^{2/3}f(x) \quad (2)$$

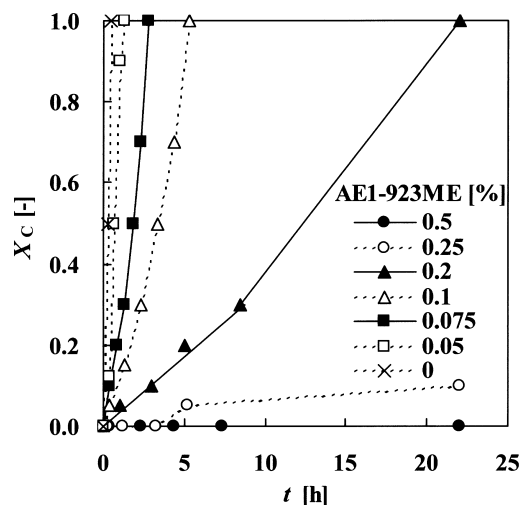


Fig. 5(a) The effects of the AE1-923ME concentration on the rate of transformation of the B-form to the C-form in 60%-E solvent at 60°C

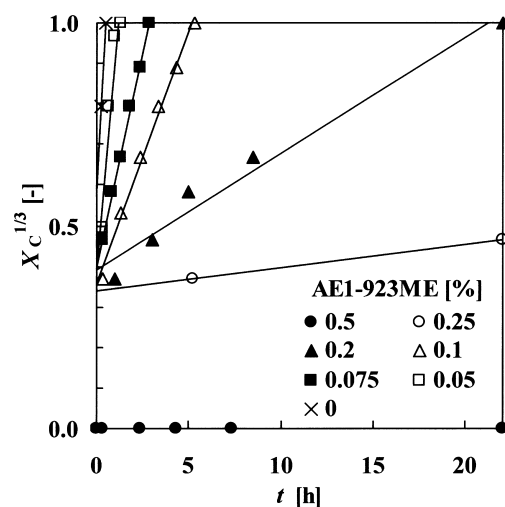


Fig. 5(b) Rearrangement of the data presented in Figure 5(a). Relationship between $X_C^{1/3}$ and transformation time t in the solvent-mediated transformation of the B-form to the C-form

where t is the transformation time (Sudo *et al.*, 1991). The k is the rate constant and $f(x)$ is the driving force for crystal growth of the C-form. For instance, $f(x)$ may be the n -th powered ΔC that is the difference in solubility between the B-form and the C-form. From the integration of Eq. (2), we obtain,

$$X_C^{1/3} = k_c(t - \theta) \quad 0 < t < \theta, \quad X_C = 0 \quad (3)$$

where k_c is the overall transformation rate constant and equal to $kf(x)/3$. The θ is the waiting time for nucleation of the stable C-form. Since in the present work, no waiting time was observed, θ should be zero. The

Table 2 Dependency of the overall transformation rate constant k_c on the concentration of AE1-923ME at 50 and 60°C

Impurity [wt%]*	k_c [h ⁻¹]	
	AE1-923ME	
	50°C	60°C
0	0.28	0.83
0.05	—	0.51
0.075	—	0.21
0.1	0.077	0.12
0.2	0	0.029
0.25	—	0.006
0.5	—	0

*based on the concentration of AE1-923

rate of transformation varies depending on the agitation rate and temperature (Maruyama *et al.*, 1999), and contamination with impurities as described in the present work. Those influences are expressed in the overall transformation rate constant, k_c . This equation has been frequently used to express the transformation rate of polymorph (Maruyama and Ooshima, 2000). Figure 5(a) was rearranged by Eq. (3) and the results were presented in Figure 5(b). Linear relationships between $X_C^{1/3}$ and t were obtained. The linear relationship indicates that the rate-determining step of the transformation is crystal growth of the stable C-form crystals. However, those straight lines did not concentrate in the origin expected from no waiting time for nucleation of the C-form crystals (namely, $\theta = \text{zero}$), but may concentrate in one point on the vertical axis ($X_C^{1/3} = 0.35$). The value of 0.35 in $X_C^{1/3}$ corresponds to 0.042 in X_C . Since the value is negligibly small, we estimate that this may be caused by experimental errors. The possible errors include an analytical error of polymorphs by IR spectroscopy and a possibility that the B-form crystals might have contained the C-form crystals less than 5 wt% before starting the transformation of the B-form. Unfortunately we cannot discuss the contamination of the C-form crystals less than 5 wt%, because the limit of detection of polymorph was approximately 5 wt% as described in the experimental section. The slope of the straight line corresponds to the overall transformation rate constant k_c . In **Table 2**, the values of k_c determined from each straight line were tabulated. The data were represented in **Figure 6**. The k_c values decreased with an increase in the concentration of AE1-923ME, but the decrease was not in direct proportion of the concentration of AE1-923ME, but in exponential.

The k_c values obtained at 50°C in 60%-E solvent were also tabulated in Table 2. Those data show that the transformation at 50°C is slower than that at 60°C

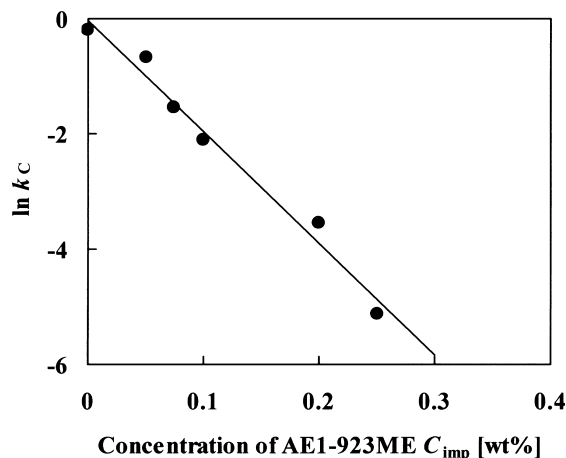


Fig. 6 Relationship between k_c at 60°C and the concentration of AE1-923ME. Straight line: $k_c = 0.86\exp(C_{\text{imp}})$, where C_{imp} is the concentration of AE1-923ME

and the slow transformation is more strongly inhibited by AE1-923ME. Namely the transformation at 50°C is completely inhibited by 0.2 wt% of AE1-923ME, while 0.5 wt% at 60°C.

2.3 Determination of the process inhibited by AE1-923ME in the solvent-mediated transformation of the B-form to the C-form

As mentioned above, the solvent-mediated transformation of the B-form to the C-form proceeds through three processes, the nucleation of the stable C-form, the crystal growth of the C-form and the dissolution of the metastable B-form. Whichever the process is inhibited by AE1-923ME, the solvent-mediated transformation will not proceed. We examined which process is inhibited by AE1-923ME.

2.3.1 Dissolution of the metastable B-form crystals

Figure 7 presents the dissolution curves of the B-form crystals in the presence and absence of 0.5 wt% of AE1-923ME. The dissolution rate was not affected by AE1-923ME. The solution concentration in the presence of 0.5 wt% of AE1-923ME reached the solubility of the metastable B-form crystals because of no transformation of the B-form to the C-form. On the other hand, the dissolution in the absence of AE1-923ME stopped at the solubility of the C-form crystals. It may be explained with the fact that a circumstance in the absence of AE1-923ME is favorable to the C-form. Indeed polymorph of the crystals recovered after 30 min was the C-form. At any rate, the dissolution test suggested that AE1-923ME inhibits the nucleation and/or crystal growth of the C-form.

2.3.2 The effect of AE1-923ME on the nucleation and growth of the C-form crystals

In order to clarify the effect of AE1-923ME on the nucleation and growth of the C-form crystals, an experiment was conducted, where the timing of AE1-923ME addition to the slurry

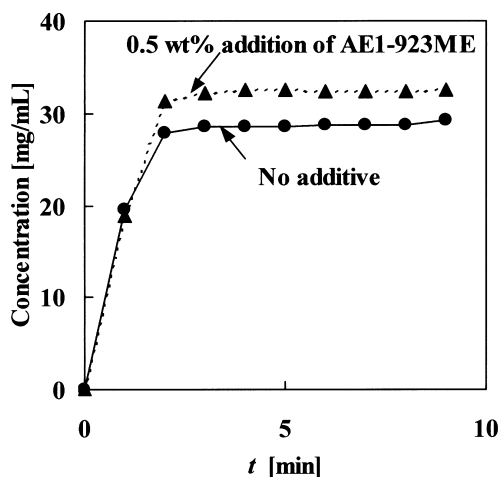


Fig. 7 Dissolution of the B-form crystals at 60°C in the presence and absence of 0.5 wt% AE1-923ME

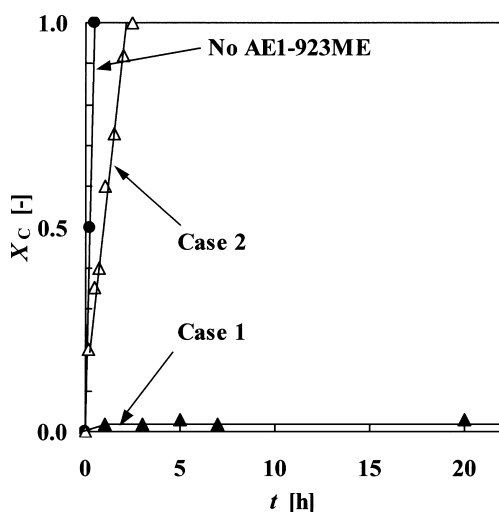


Fig. 8 The effect of the timing of the addition of AE1-923ME to the slurry of the B-form crystals in the transformation of the B-form to the C-form in 60%-E solvent at 60°C. Addition timing: Case 1, before the B-form crystals began to transform to the C-form crystals; Case 2, on the way of the transformation

of the B-form crystals was changed. First, AE1-923ME was added before the B-form crystals began to transform to the C-form crystals (Case 1). Another addition was carried out on the way of transformation (Case 2). The experimental results were presented in **Figure 8**. When AE1-923ME of 0.5% was added before the B-form crystals began to transform to the C-form crystals, the transformation of the B-form crystals never proceeded. On the other hand, when AE1-923ME was added after 20%-transformation, the transformation of the B-form crystals continued to proceed, although the

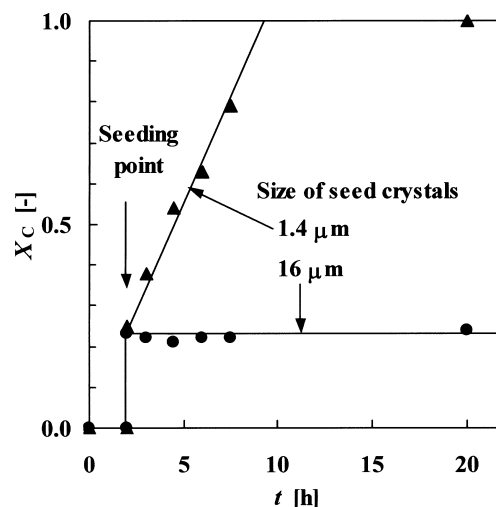


Fig. 9 The effect of the C-form seed crystals on the transformation of the B-form crystals in the presence of AE1-923ME in 60%-E solvent at 60°C

transformation rate was slightly decreased. These results mean that AE1-923ME does not inhibit the crystal growth of the C-form but preferentially inhibits the nucleation of the C-form crystals. In order to confirm this, another experiment was conducted as mentioned in the experimental section. **Figure 9** shows the effect of the C-form seed crystals on the transformation of the B-form crystals in the presence of AE1-923ME. When the large seed crystals were used, the transformation of the B-form did not proceed. However, when the small seed crystals were used, the B-form crystals completely transformed to the C-form crystals, although the transformation rate was slow. This experiment confirmed the conclusion obtained in **Figure 8** that even when the C-form crystals are present in solution, their growth proceeds, regardless of the presence of AE1-923ME. However, it is unknown why the large crystals were not active as seed crystals. Since as long as observed with an optical microscope, size of the C-form crystals obtained using small seed crystals was almost the same as that of the crystals obtained in the absence of AE1-923ME, namely about 16 μm , the limitation of growth may be present.

Figure 10 shows the Arrhenius plots of the overall transformation rate constants obtained in the absence and presence of 0.1 wt% AE1-923ME. The activation energy was determined to be 75.0 kJ/mol. Since the rate-determining step of the transformation is the growth of the C-form crystals, the activation energy determined should be that of the crystal growth of the C-form. The same value was obtained regardless of the absence and presence of AE1-923ME. This is another evidence that AE1-923ME does not inhibit the growth of the C-form crystals.

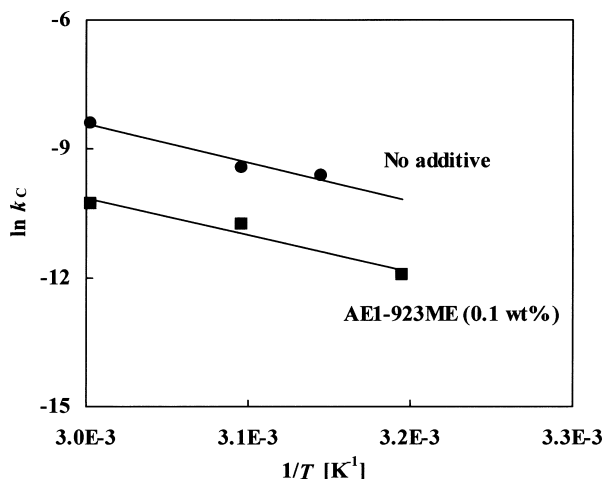


Fig. 10 Arrhenius plots of the overall transformation rate constants obtained in the absence and presence of 0.1 wt% AE1-923ME

Conclusions

The effect of impurities on the solvent-mediated transformation of crystal polymorphs of a drug substance AE1-923 was investigated. AE1-923 was developed for an indication of pollakiuria and pain. It has three polymorphs, namely the unstable A-form, the metastable B-form and the stable C-form.

An intermediate, AE1-923ME, in the synthesis of AE1-923 inhibited the transformation of the B-form crystals to the C-form crystals, but the transformation of the A-form to the B-form was not inhibited. As mentioned above, a solvent-mediated transformation proceeds through three processes, the nucleation of the stable form, the crystal growth of the stable form and the dissolution of the metastable form. AE1-923ME of 0.5 wt% completely inhibited the nucleation of the stable C-form crystals. The results shown in Figures 8, 9, and 10 suggested that AE1-923ME does not inhibit the crystal growth of the C-form.

The inhibitory effect of AE1-923ME was evaluated by the overall transformation rate constant k_c . As a result, it was found that the inhibitory effect of AE1-923ME exponentially increases with an increase in its concentration as shown in Figure 6. As long as the inhibitory effect was evaluated with a minimum concentration of AE1-923ME at which the transformation of the B-form to the C-form was completely inhibited, the inhibitory effect at 50°C was larger than that at 60°C.

Acknowledgment

This study was conducted as part of the SINC-PRO project "Intelligent Design and Control of Batch Crystallization Process" in the IMS (Intelligent Manufacturing Systems) program and also as part of Nanotechnology Materials Program "Systematization of Nanotechnology Program Results Project", which was financially supported by the New Energy and Industrial Technology Development Organization (NEDO) in Japan.

Nomenclature

$f(x)$	= driving force for crystal growth of the C-form	[—]
k	= transformation rate constant	[h ⁻¹]
k_c	= overall transformation rate constant	[h ⁻¹]
t	= transformation time	[h]
W_B	= weight of the B-form crystals contained in product crystals	[kg]
W_C	= weight of the C-form crystals contained in product crystals	[kg]
X_C	= weight ratio of the C-form crystals defined by Eq. (1)	[—]
θ	= waiting time	[h]

Literature Cited

- Audran, M., Y. Lasserre, J. Rambaud, B. Pauvert, G. Berge and L. Maury; "Comparative-Study of *in vitro* Dissolution and Bone Absorption of Sulfamethadine and One of Its Solvates," *Pharm. Acta Helv.*, **63**, 343–346 (1988)
- Davey, R. J., N. Blagden, G. D. Potts and R. Docherty; "Polymorphism in Molecular Crystals: Stabilization of a Metastable form by Conformational Mimicry," *J. Am. Chem. Soc.*, **119**, 1767–1772 (1997)
- Domopoulou, A., A. Michaelides, S. Skoulika and D. Kovala-Demertzi; "Crystallization of an Unstable Molecular Compound Using a Tailor-Made Additive," *J. Crystal Growth*, **191**, 166–168 (1998)
- Kato, Y., Y. Okamoto, S. Nagasawa and T. Ueki; "Solubility of a New Polymorph of Phenobarbital Obtained by Crystallization in the Presence of Phenytoin," *Chem. Pharm. Bull.*, **29**, 3410–3413 (1981)
- Kuroda, K., T. Yokoyama, T. Umeda, Y. Kita, A. Konishi and T. Kuroda; "Studies on Drug Nonequivalence VIII. Solubilities of Polymorphs and Hydrate of Mercaptopurine," *Yakugaku Zasshi*, **99**, 745–751 (1979)
- Maruyama, S. and H. Ooshima; "Crystallization Behavior of Taltirelin Polymorphs in a Mixture of Water and Methanol," *J. Crystal Growth*, **212**, 239–245 (2000)
- Maruyama, S., H. Ooshima and J. Kato; "Crystal Structures and Solvent-Mediated Transformation of Taltirelin Polymorphs," *Chem. Eng. J.*, **75**, 193–200 (1999)
- Okamoto, M., M. Hamano and H. Ooshima; "Active Utilization of Solvent-Mediated Transformation for Exclusive Production of Metastable Polymorph Crystals of AE1-923," *J. Chem. Eng. Japan*, **37**, 95–101 (2004)
- Sudo, S., K. Sato and Y. Harano; "Growth and Solvent-Mediated Phase Transition of Cimetidine Polymorphic Forms A and B," *J. Chem. Eng. Japan*, **24**, 628–632 (1991)
- Yokoyama, T., T. Umeda, K. Kuroda, T. Kuroda and S. Asada; "Studies on Drug Nonequivalence X. Bioavailability of 6-Mercaptopurine Polymorphs," *Chem. Pharm. Bull.*, **29**, 194–199 (1981)