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Particle Design of Tolbutamide by the Spherical Crystallization Technique. II. Factors Causing Polymorphism of Tolbutamide Spherical Agglomerates

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Tolbutamide (TBM) was agglomerated by several methods of spherical crystallization technique. A mixture of an ethanolic solution of TBM (II) and isopropyl acetate (III: bridging liquid) was added to water (I: crystallization solvent), and crystals were allowed to form. Agglomeration was then allowed to proceed while this system was stirred at 600 rpm. Next, I was added to a mixture of II and III; that is, the order of addition in the initial procedure was reversed, and crystallization–agglomeration was carried out. In addition, after adding I to II and causing the crystallization of TBM, III was added to the system to bring about agglomeration.

These different crystallization–agglomeration techniques yielded TBM agglomerates having different crystalline forms, with a mixture of form A and form B obtained in the mixed solution of ethanol/water/isopropyl acetate (the first 2 methods described above) and form B obtained in the mixed solution of ethanol/water (the 3rd method). The composition ratio of the mixture of form A and form B crystals also differed as a function of the crystallization process. The findings of these experiments indicated that the causes of this difference in the composition ratio differ as a function of the course of changes in the composition of the TBM solution up to the point of agglomeration due to difference in the crystallization method. That is, it was elucidated that the crystalline form of the TBM agglomerate depends on the solvent environment (composition) at the time of formation of the crystal nuclei.

Keywords tolbutamide; polymorphism; spherical crystallization technique; X-ray diffraction; particle design; recrystallization

The authors have developed the spherical crystallization technique, in which crystallization and agglomeration are carried out simultaneously.[1)] This technique affords spherically-agglomerated microcrystals and is a new particle design method by which it is possible to combine the processes of crystallization and granulation as well as to improve such powder properties of chemicals as their flowability and filling properties.[2,3)]

Simmons *et al.*[4)] reported that tolbutamide (TBM) crystallized out of a mixture of benzene and hexane as form A crystals and out of an ethanol/water mixture as form B crystals. They also reported that, although form A and form B showed equivalent solubility and bioavailability, form B readily underwent powder bridging in the hopper and capping at the time of tableting. In addition, it is known that—in general—crystalline polymorphs exhibit significant differences in compressibility, solubility, bioavailability, *etc.*[5,6)] Accordingly, crystalline polymorphism exerts a great influence on these secondary characteristics of crystals, and it is therefore very important to control polymorphism during the crystallization process.[7,8)] Since the spherical crystallization technique involves crystallization, by controlling the crystallization process it is possible to obtain a crystalline form having advantageous secondary characteristics. In the present research, TBM was selected as the test pharmaceutical, and various crystallization processes were applied to prepare polymorphic crystalline forms of TBM. The objective of these studies was to elucidate the factors causing polymorphism of TBM spherical agglomerates.

Experimental

Crystallization Method A As shown in Figs. 1 and 2, 250 ml of water (I: crystallization solvent) was placed in the cylindrical vessel of the apparatus, followed by addition of 65 ml of a mixture comprised of 50 ml of ethanol solution (II) in which 5 g of TBM was dissolved and 15 ml of isopropyl acetate (III: bridging liquid) while stirring at 600 rpm with a turbine-type agitator to bring about crystallization, and agglomeration was then carried out for 40 min at a temperature of 25 ± 1 °C. In addition, using the same mixing ratio of II and III, the volume of this mixture added to 250 ml of I was varied from 39 to 6.5 ml, and the subsequent processing was the same as above.

Crystallization Method B A mixture comprised of 50 ml of II containing TBM and 15 ml of III was placed in the cylindrical vessel of the apparatus and, while stirring, 250 ml of I was added; agglomeration was performed by the same procedure as in method A above. In addition, the volume of I added to the 65 ml mixture of II and III was varied between 200 and 50 ml, followed by agglomeration in the same manner (Figs. 1 and 2).

Crystallization Method C A suspension consisting of 250 ml of I and 15 ml of III was placed in the cylindrical vessel of the apparatus and, while stirring, 50 ml of II containing TBM was added; agglomeration was then achieved by the same process as in method A (Figs. 1 and 2).

Crystallization Method D Ethanol (II; 50 ml) containing TBM was placed in the cylindrical vessel of the apparatus and, while stirring, a suspension consisting of 250 ml of I and 15 ml of III was added. TBM was crystallized, and agglomeration was then achieved by the same process as in method A (Figs. 1 and 2).

Crystallization Method E Ethanol (II; 50 ml) containing TBM was placed in the cylindrical vessel of the apparatus and, while stirring, 250 ml of I was added to cause crystallization of TBM. Immediately thereafter and after 30 s, 1 and 2 min, 15 ml of III was added, and agglomeration was then achieved by the same process as in method A. In addition, the volume

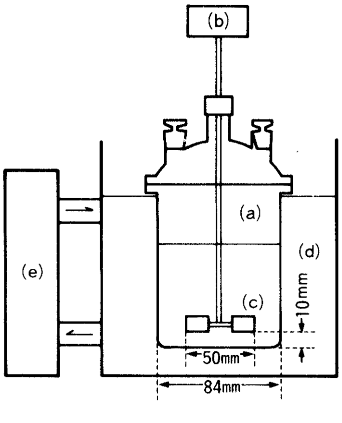

Fig. 1. Apparatus for Spherical Crystallization of Tolbutamide

(a) Cylindrical vessel (500 ml), (b) motor, (c) turbine-type agitator (6 blades, agitation speed 600 rpm), (d) water bath (temperature 25 ± 1 °C), (e) regulator.

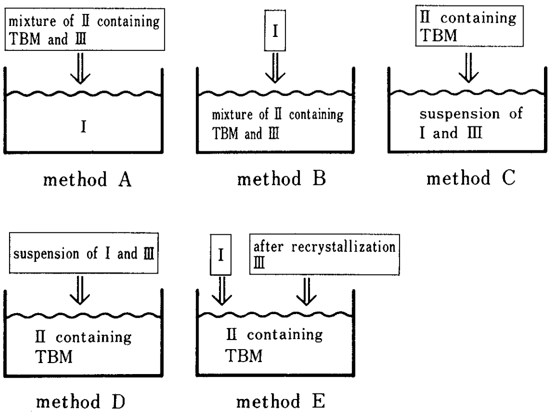

Fig. 2. Technique for Spherical Crystallization of Tolbutamide

of III added to the system 30 s after crystallization was varied between 10 and 0.2 ml, with the rest of the process remained the same as above (Figs. 1 and 2).

Recrystallization of TBM from Mixed Solvent Various solvent mixtures of water/ethanol and water/ethanol/isopropyl acetate were prepared by varying the mixing ratios of the components. TBM was then dissolved in those mixtures at 50 °C, followed by standing at 25 °C to permit recrystallization of the TBM from the solutions.

X-Ray Diffraction Analysis The crystals were subjected to X-ray diffraction analysis (model PW1710, Philips Co.) under the following conditions: Cu target, monochromator, scintillation counter, voltage 40 kV, current 30 mA, receiving slit 0.3 mm, time constant 1 s, full scale 10000 cps, and scan speed 1.5° 2θ/min.

Results and Discussion

Determination of Composition of Polymorphic Forms in TBM Crystal Mixture by X-Ray Diffraction As shown in Fig. 3, form A of TBM showed $2\theta = 12.2°$, while form B showed $2\theta = 11.4°$. The intensity (peak height) of each specific peak was determined, and then, in accordance with Robert's method,[9] the equation shown below was employed to calculate the mixing ratio of form A in the TBM agglomerate.

Form A and form B crystals of TBM were prepared by the methods of Simmons *et al.*,[4] and mixtures containing these 2 forms in various ratios were then prepared. Using those known mixtures, a calibration curve was prepared. The calibration curve was linear and passed through the origin, and the application of the equation was thus successful.

$$\text{mixing ratio of form A} = \frac{1}{1 + \frac{1}{K} \times \frac{I_{\mathrm{B}} - I_{\mathrm{B'}}}{I_{\mathrm{A}} - I_{\mathrm{A'}}}}$$

$$1/K = (I_{\mathrm{A50}} - I_{\mathrm{A'}})/(I_{\mathrm{B50}} - I_{\mathrm{B'}})$$

I_{A}: peak intensity at 12.2° of sample
I_{B}: peak intensity at 11.4° of sample
$I_{\mathrm{A'}}$: peak intensity of form A at 11.4°
$I_{\mathrm{B'}}$: peak intensity of form B at 12.2°
I_{A50}: peak intensity at 12.2° of 1 : 1 mixture of forms A and B
I_{B50}: peak intensity at 11.4° of 1 : 1 mixture of forms A and B

Crystalline Form of TBM Agglomerates Obtained by Crystallization Methods A through E With each of the crystallization methods A through E, the microcrystals of TBM were aggregated to form spherical agglomerates having particle sizes ranging from *ca.* 100 to *ca.* 800 μm.

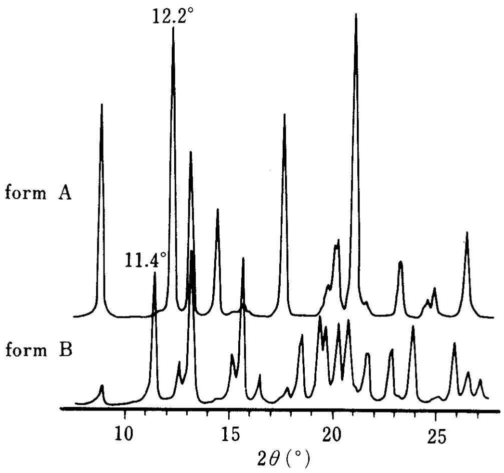

Fig. 3. X-Ray Diffraction Patterns of Tolbutamide Form A and Form B

As shown in Table I, the crystalline agglomerates that were obtained by methods A—D consisted of mixtures of form A and form B crystals of TBM. The mixing ratio of form A and form B was found to differ with the crystallization method, and more form B crystals were formed by method B than by methods A, C or D. It was thus learned that the order of addition of water, ethanol and isopropyl acetate affects the formation of crystals. In methods A and C, TBM crystallization was brought about by adding a good solvent (ethanol/isopropyl acetate or ethanol), in which TBM had been dissolved, to a poor solvent (water or a suspension of water and isopropyl acetate). That is, simultaneously with the addition of the good solvent containing dissolved TBM, the crystallization of TBM began, and then—as depicted in Fig. 4—the solution composition with method A shifted from X to agglomeration point S, while with method C it shifted from X′ to S. On the other hand, in methods B and D, the poor solvent is added to the good solvent containing dissolved TBM. In the case of method B, the solution composition, as shown in Fig. 4, is shifted from Z′ through R (crystallization point of TBM in method B) to S. Between Z′ and R, TBM is in the dissolved state, while from R it is in crystalline form. The solution composition of method D changes from Y to S. In this manner, it was demonstrated that changes in the solution composition and the course of TBM crystallization differ as a function of the procedures in methods A through D. That is, these findings indicate that the crystallization of TBM depends on the method of addition of the solvents and also that the form of the crystals depends on the composition of the water/ethanol/isopropyl acetate mixture at the time of formation of the crystal nuclei.

On the other hand, with method E, when the isopropyl acetate was added immediately after or 30 s after the crystallization of TBM, the agglomerate showed almost the same composition ratio of form A and form B crystals as the ratios which were obtained with methods A—D. However, when the addition of isopropyl acetate was delayed until 1 or 2 min after crystallization, the agglomerate consisted mostly of form B crystals. Thus, the time of addition of isopropyl acetate exerted a great effect on the form of TBM crystals (Table I). That is, in method E, water was added to the ethanol solution containing dissolved TBM, and after TBM crystallization (*i.e.*, immediately after, and 30 s, 1 or 2 min after) isopropyl acetate was added to the system. As shown in Fig. 4, the composition of the

TABLE I. Composition Ratios of Polymorphic Crystals in TBM Agglomerates Resulting from Various Crystallization Methods

	Method A	Method B	Method C	Method D	Method E			
					Immediately	30 s	1 min	2 min
Crystal form	A : B	A : B	A : B	A : B	A : B	A : B	A : B	A : B
Composition form	9 : 1—8 : 2	8 : 2—5 : 5	9 : 1—8 : 2	8 : 2—7 : 3	9 : 1—7 : 3	9 : 1—5 : 5	1 : 9—0 : 10	0 : 10

TABLE II. Composition Ratios of Polymorphic Crystals in TBM Agglomerates Formed at Time of Agglomeration in Solutions with Various Mixing Ratios

Method A			Method B			Method E		
Aggl. point	EtOH ratio (%)	A : B	Aggl. point	Water ratio (%)	A : B	Aggl. point	IA ratio (%)	A : B
E1	1.5	3 : 7	W1	56	1 : 9	I1	0.2	0 : 10
E2	3.0	6 : 4	W2	66	1 : 9	I2	0.9	4 : 6
E3	5.8	9 : 1	W3	74	2 : 8	I3	1.5	8 : 2
E4	8.3	9 : 1	W4	79	3 : 7	I4	2.9	9 : 1

Aggl. = agglomeration. IA = isopropyl acetate. E1—E4, W1—W4 and I1—I4 indicate the respective composition points (agglomeration points) shown in Fig. 5.

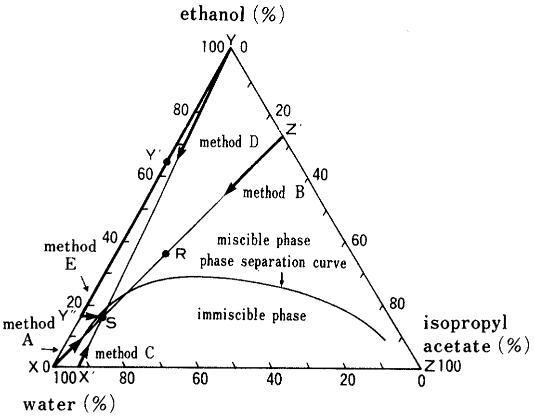

Fig. 4. Diagram of TBM Crystallization Methods

S, agglomeration point; R, TBM crystallization point in method B; Y′, TBM crystallization point in method E; Y″, point of addition of isopropyl acetate in method E.

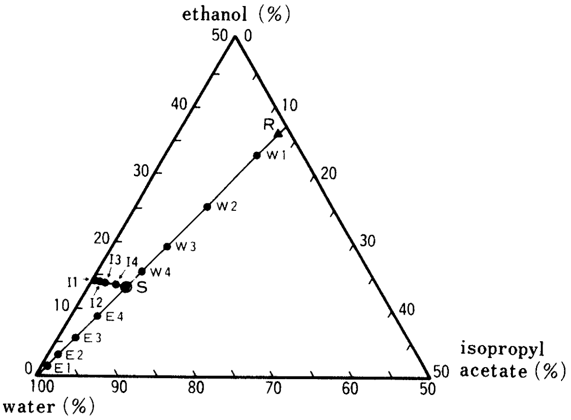

Fig. 5. Composition Ratios at Time of Agglomeration in Methods A, B and E

E1—E4, method A; W1—W4, method B; I1—I4, method E; S, agglomeration point; R, TBM crystallization point in method B.

solution passed from Y through Y′ (the point of TBM crystallization in method E), and then shifted to Y″ (the point of addition of isopropyl acetate in method E) as crystallization occurred. Then, isopropyl acetate is added to the system at point Y″, and the solution composition shifts to S. However, because the time of addition of isopropyl acetate was varied, as the time of addition of isopropyl acetate became earlier, the duration of the state at Y″ became shorter and the shift to S was quicker whereas Y″ was maintained for a longer time as the addition of isopropyl acetate was delayed. That is to say, with method E, an early time of addition of isopropyl acetate to the system means that TBM crystallizes out in the 3 components (water, ethanol and isopropyl acetate), while the late addition of isopropyl acetate means that TBM crystallizes out of 2 components (water and ethanol). Therefore, even with method E, the composition ratio of the solution at the time of formation of the crystal nuclei is deeply involved in determining the form of the TBM crystals, as in the cases of methods A through D.

Effects of Water, Ethanol and Isopropyl Acetate on Form of TBM Crystals With the objective of further elucidating the above phenomena, as shown in Fig. 5, agglomeration of TBM crystals was carried out at all composition points except for S, and the influence of the composition ratio of the solution on the form of the crystals was investigated. That is, in method A, an ethanol/isopropyl acetate mixture containing dissolved TBM was added to water, and the concentration of ethanol in the system thus increased gradually (0→8.3%); therefore, the mixing ratio of ethanol was varied, and agglomeration occurred between E1 and E4. In addition, in method B, the reverse approach was taken: since water was added to the system, the concentration of water gradually increased (0→79%), and as the amount of added water changed, agglomeration occurred between W1 and W4. Moreover, in method E, water was added to the ethanolic solution containing dissolved TBM, and TBM was crystallized out; then, 30 s later the isopropyl acetate was added to the system in various amounts, and agglomeration occurred between I1 and I4.

(a) Effects of Ethanol and Water in Methods A and B As shown in Table II, in method A, the increase in the concentration of ethanol in the system was accompanied

Table III. Composition Ratios of Polymorphic Crystals of TBM upon Recrystallization

Recry. point[a]	Method A	Method B							Method D		Method E					
		S	B1	B2	B3	R	B4	B5	D1	D2	Y′	E	Y″	X	Y	Z
Form A	4—8	9—10	8—2	8—2	0	0	0	0	0	0	0	0	0	10	10	10
Form B	6—2	1—0	2—8	2—8	10	10	10	10	10	10	10	10	10	0	0	0

[a] Recrystallization point: the various composition points of the solution for recrystallization of TBM, shown in Fig. 6.

with an increase in the ratio of formation of form A crystals of TBM. In method B, the increase in the concentration of water in the system was accompanied with a decrease in the formation of form B crystals. The agglomerates obtained at E4 (method A) and W4 (method B) were found to have a form A : form B composition ratio which was similar to the composition ratio of the respective agglomerates obtained at S in both methods. In addition, with method B, when the water concentration exceeded R (53%), TBM crystallized out. Investigation of the form of the crystals obtained at composition points W1 and W2 near R showed them to be almost entirely form B. It was thus learned that TBM is crystallized in form B in the vicinity of R. On the basis of these findings, it is clear that a large influence is exerted on the form of the crystals by the concentration of ethanol in method A and the concentration of water in method B. Thus, it was elucidated that the crystalline form of TBM depends on the composition of the solution at the time of crystallization.

(b) Effect of Isopropyl Acetate in Method E When isopropyl acetate was added to the system 30 s after crystallization of TBM, as the concentration of isopropyl acetate increased and the composition ratio approached S, the ratio of form A in the TBM agglomerate increased. This result is similar to that observed with methods A and B. In addition, at I1, where the concentration of isopropyl acetate can be ignored, only form B crystals of TBM were formed. Also, as shown in Table I, as the time of addition of isopropyl acetate was delayed, only form B crystals were obtained. These 2 facts indicate that TBM crystallizes out of a water–ethanol mixture as form B crystals. In this way, it was elucidated that the form of the crystals of TBM is dependent on the composition of the solution at the time of crystallization, even in the case of method E.

Form of Crystals Obtained by Recrystallization As shown in Fig. 6, TBM was recrystallized from solution, and those results are compiled in Table III. In the 3-component system of water/ethanol/isopropyl acetate, form B crystals were formed in the vicinity of R, a mixture of form A and form B crystals was formed as the system approached point S, and at S the mixture of form A and form B consisted almost entirely of form A crystals. On the other hand, in the 2-component system of water and ethanol, the TBM crystals were always form B.

These results coincide with the results obtained when the mixing ratio of the solvents in the system was varied and agglomeration was caused to occur. These results thus support the deductions drawn to date and the theory which has been proposed.

Factors Causing Polymorphism On the basis of the experimental results described above, the following factors have been elucidated as causing the polymorphism of TBM crystals occurring in methods A through E for achieving spherical crystallization and agglomeration.

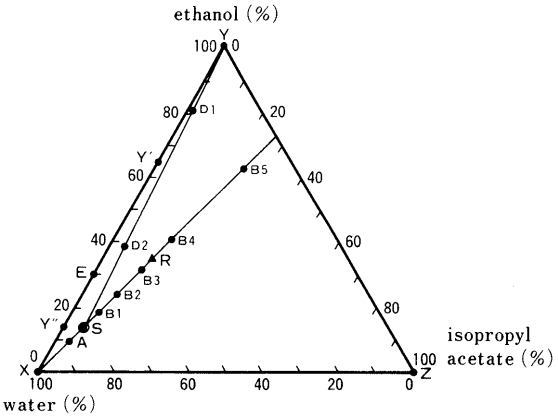

Fig. 6. Composition Ratios in Recrystallization System

A, method A; B1—B5, method B; D1—D2, method D; E, Y′ and Y″, method E; S, agglomeration point; R, TBM crystallization point in method B.

(a) Method A In this system, crystallization of TBM occurs simultaneously with the addition of the ethanol/isopropyl acetate mixture, and most of the TBM has been crystallized out by the time the composition of the system reaches point S (the point at which the addition of 65 ml of the ethanol/isopropyl acetate mixture has been completed) (Fig. 4). That is, the composition of the system reaches S immediately, and form A crystal nuclei of TBM begin to be formed (a small amount of form B crystals is also formed); thereafter, the crystal nuclei grow to form form A crystals. On the other hand, since TBM is dissolved in the ethanol/isopropyl acetate mixture, at the interface, the composition of the system changes from Z′ through R (this is the point where crystallization begins in method B) and, while crystallization is occurring, reaches S. That is, at the interface, when the system has passed through R, only form B crystals are formed, but form A crystals also begin to be formed as the composition changes. At these compositions, nuclei of both form A and form B crystals are formed. Accordingly, with method A, in the system as a while almost all of the TBM is crystallized out as form A, but since a small amount of form B crystals is formed at the interface, a mixture of form A and form B crystals is obtained. Nevertheless, that crystalline mixture consists predominantly of form A crystals.

(b) Method B As in the case of the change in the composition at the interface in method A, in method B the system shifts from Z′ through R and is then changed to S (Fig. 4). In other words, in this system TBM is in the dissolved state from Z′ through R, and at the point that it has passed through R, the nuclei for only form B crystals begin to form. Then, accompanying the change in the composition, form A crystal nuclei also begin to form, so that at S almost all of the nuclei are form A. Next, these crystal nuclei pass through a period of growth and both form A and form B crystals are formed. Crystallization occurs especially at S, and thus form A crystals predominate over form B crystals in the mixture. There is then the question of why the composition ratio of form B crystals is higher with method B than with method A. The explanation is thought to be that, whereas in method A the formation of form B crystal nuclei occurs only at the interface, in method B form B crystal nuclei are formed throughout the system.

(c) Method C The changes in the system of method C can be understood on the basis of an explanation similar to that presented above for method A. That is, in this system, while crystallization occurs from point X′, the composition changes to that at S (Fig. 4). Throughout the system, TBM crystallizes out of the solution at S, and most of the crystals are form A. Then, at the interface, the composition shifts from Y to S, and in the vicinity of Y′ a very small amount of form B crystals is formed. As a result, similar to the case of method A, a mixture of form A and form B crystals is obtained, but form A crystals predominate.

(d) Method D The changes in the system of method D can be explained in the same manner as the system of method B. That is, the composition of the system changes from Y to S, passing in the vicinity of Y′ (Fig. 4). In the vicinity of Y′, TBM crystallizes out of the solution as form B crystals, while in the vicinity of S, form A crystals are formed, resulting in a mixture of form A and form B crystals. The reason why the composition ratios of the TBM crystalline mixtures obtained in method C and method D differ is thought to be similar to the explanation offered for the difference between method A and method B: the difference between the interface and the system as a whole.

(e) Method E In this system, the composition of the mixture changes from Y to Y′ (in method E, this is the point at which crystallization of TBM begins), and then to Y″ as crystallization occurs. Since isopropyl acetate is added to the system at point Y″, the composition of the system changes to S (Fig. 4). When the isopropyl acetate is added to the system 2 min after the point in time when the composition of the system has become that at Y″, form B crystal nuclei are formed during the shift from Y′ to Y″. The composition at Y″ is within the stable zone of form B crystals, and the formation of crystal nuclei continues for approximately 1—2 min. Thereafter, the system enters the period of growth of TBM crystals, and form B crystals are formed. That is, since isopropyl acetate is added after 2 min, the composition of the system changes from Y″ to S. However, at the time when isopropyl acetate is added (2 min after crystallization), the formation of form B crystal nuclei has been completed, and since point S is in the period of growth of form B crystals, the formation of form A crystal nuclei no longer occurs and only form B crystals are formed. On the other hand, when isopropyl acetate was added to the system immediately after, 30 s after and 1 min after the point at which the system composition reached Y″, the ratio of form A crystals in the TBM crystalline mixture increased as the time of addition was advanced. That is, form B crystals nuclei are formed immediately after crystallization at Y″, but if the isopropyl acetate is added to the system prior to the completion of the TBM crystallization, the composition of the system changes from Y″ to S and the remaining dissolved TBM crystallizes out of the system at S. In other words, the dissolved TBM forms form A nuclei which then grow, and a mixture of form A and form B crystals is obtained. That is, the ratio of form A crystal nuclei formed is dependent on the time until the composition of the system changes from Y″ to S. Therefore, as the time at which isopropyl acetate is added to the system is advanced, the formation of form A crystal nuclei becomes greater than the formation of Form B crystal nuclei, and the amount of form A crystals increases.

Conclusion

The factors causing polymorphism of TBM crystals were found to differ as a function of the course of changes in the composition of the TBM solution up to the point of agglomeration due to differences in the crystallization method. That is, it was elucidated that the crystalline form of the TBM agglomerate obtained by the method employed depends on the solvent environment (composition) at the time of formation of the crystal nuclei. The spherical crystallization technique makes it possible to obtain the desired form of crystals of TBM by controlling the composition of the solution, and so is a valuable technique for particle design.

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