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Polymorphism of D-mannitol: Crystal structure and the crystal growth mechanism☆

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ABSTRACT

The polymorphism of D-Mannitol (mannitol) is reviewed in this paper. It was found that the structure of the stable form is consistent in most literatures, but different authors have given different information about the two metastable forms. Therefore the commonly used nomenclature of mannitol was summarized based on the crystal unit cell parameters with the help of X-ray powder diffraction. Moreover, the crystal growth mechanism of mannitol polymorphs was summarized. Considering the lack of kinetic data for the metastable form especially, a reported method was attempted to apply to δ mannitol in an aqueous cooling crystallization process based on the induction time previously measured, and it was identified that the growth of the δ form follows the two-dimensional (2D) nucleation-mediated mechanism. The results also indicate that the method based on induction time and supersaturation should have the potential to be expanded to the metastable polymorphs for the growth property study in a bulk system. © 2016 The Chemical Industry and Engineering Society of China, and Chemical Industry Press. All rights reserved.

1. Introduction

Polymorphism, defined as the ability of a material to crystallize in different crystal structures, has gained more and more attention especially in the field of pharmaceuticals [1]. It has been reported that 80% of the marketed pharmaceuticals exhibit polymorphs under experimentally accessible conditions [2], and some of them even showed different functionalities and bioavailabilities from the previously launched products. D-mannitol (mannitol) is a natural hexahydric alditol which has been widely used in pharmaceutical industry as a nephropathy treatment medicine and also an excipient in the formulation of various tablets and granulated powders [3]. In addition to those, mannitol is a commonly used sugar replacer in food industry. The molecular structure of D-mannitol is shown in Fig. 1.

It has been reported that mannitol has three anhydrous polymorphs [4–6] and a hemihydrate [7]. However the nomenclature of mannitol polymorphs is often diverse in different literatures [8,9] in despite of some similar unit cell parameters based on X-ray powder diffraction (XRPD). Therefore a review of mannitol polymorphism is initially presented along with the preparation procedures of different forms.

Crystallization kinetics is more complicated when polymorphism is involved since on one hand, all polymorphs compete to nucleate at certain supersaturation [10,11], and on the other hand, a metastable form has

thermodynamic tendency to transform to the stable one [12], which could somehow affect the crystal growth process [13–15]. Therefore it is difficult to investigate the crystal growth kinetics especially for a metastable polymorph [16–18]. For example, in the research of Scholl *et al.* [19] a traditional desupersaturation was used to determine the growth kinetics of metastable α -glutamic acid, but it only worked at low temperature when the solvent-mediated polymorphic transformation (SMPT) could be ignored. Thus the research to the crystal growth of mannitol polymorphs was reviewed in this work for a clear perspective. Furthermore a method reported by Kuldipkumar [20] was extended to show the growth mechanism of metastable δ mannitol based on our previously collected data.

2. Polymorphism of D-mannitol

It has been confirmed that there are only three pure anhydrous polymorphs of mannitol even though numerous names have been given [6,8]. Hereby, for clarity and to avoid any confusion, the unit cell parameters of these mannitol polymorphs are summarized in Table 1. It is clear in Table 1 that the first six β references have a similar structure, which is named β in our work. While focusing on the polymorphs from the 7th to 9th in Table 1, the parameters were nearly the same disregarding what they were called in the original literature. So this form is referred to as α mannitol here. Finally, the last three items are significantly distinct from the others, and they are referred to as the δ form of mannitol in this paper.

The polymorphism of D-mannitol was firstly reported in Groth's work [27] in 1910. Then as X-ray technology started to be introduced into the analysis of crystal structures, Marwick [21] examined the X-ray pattern of the stable β form in 1931 as shown in Table 1. The

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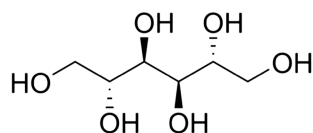


Fig. 1. Molecular structure of D-mannitol.

results were consistent with those in a subsequent paper [22] in 1952. Then in 1968, the single crystal data of the β form crystallized from an aqueous ethanol solution were confirmed by X-ray diffraction (XRD) with $\text{CuK}\alpha$ radiation by Berman *et al.* [23]. Following, a new XRD instrument (with $\text{MoK}\alpha$ radiation) was used by Kaminsky [24] to determine and refine the same polymorph in 1997, and the similar crystal lattice parameters and an improved R -value were obtained. Thus based on the consistent crystal unit cell parameters and mostly used names in the literatures shown in Table 1, it is reasonable to name these structures β form.

The α form of mannitol was also mentioned by Groth [27] in 1910, but the unit cell parameters were first given by Walter-Levy [4] in 1968 as shown in Table 1. In the same year, a slow evaporation of mannitol and boric acid solution in methanol was applied to get the α form (named K in the original literature) by Kim *et al.* [25]. In addition to the similar unit cell parameters in Table 1, a thermoanalytical study performed by Pitkanen *et al.* [28] also confirmed that the α form in Walter-Levy's work is the same with the K form in Kim's work. Moreover, the unit cell data are also found consistent with those collected by Fronczek *et al.* [5] in 2003. It is worth noting that Rey *et al.* [22] obtained a mannitol polymorph named α in 1952, while Berman *et al.* [23] prepared one named α' in 1968. The two substances have similar structure according to Berman *et al.* [23], but they should not be the α form of mannitol defined in our work since Grindley *et al.* [29] have testified by C-MNR that those two forms have different structures with the classical α form in Walter-Levy's work. Grindley *et al.* also mentioned that those two forms might be the δ form produced by Walter-Levy, but we think it is not appropriate due to the different crystal symmetry between these two (monoclinic) and the δ form (orthorhombic). Therefore it is reasonable to believe that these two forms might be mixtures. Based on Table 1, it is clear that the β and α forms of mannitol belong to the same crystal system (orthorhombic) and the same $\text{P2}_1\text{2}_1\text{2}_1$ space group with only a little difference on the length of the unit cell edges. Thus the two forms should have the same molecular conformation but different orientations of the hydrogen in the hydroxyl groups and hydrogen bonds [28].

The δ form of mannitol is difficult to isolate compared to the other two. It was firstly obtained by Walter-Levy [4] by gradual evaporation of a mannitol aqueous solution in a watch glass in 1968, where the calculated crystal lattice parameters from the XRPD data showed that

it belongs to P2_1 space group as illustrated in Table 1. However this procedure was found difficult to follow as other researchers [30] could only obtain a mixture of the δ and α forms instead of pure δ mannitol with the same method. Pitkanen *et al.* [28] then prepared δ mannitol by slow cooling a pure melt in 1993, still different polymorphs or mixtures were obtained while the cooling rate fluctuated. Then a freeze-dryer was finally applied to get the δ form with high reproducibility [26,31]. After that, a handy anti-solvent crystallization [6] was reported to produce the δ form (named form III in the original literature), during which the solid had to be filtered and dried immediately in order to prevent any polymorphic transformation. Recently, Sullivan *et al.* [32] successfully produced δ mannitol by cooling a saturated solution rapidly in dilute aqueous ethanol to below 0°C . In all the work mentioned above, the unit cell parameters or XRPD patterns of δ form are consistent to those shown in Table 1. It is also clear in Table 1 that the δ form displayed significant difference in the hydrogen bond situation from the previously known α and β forms. In 2003, the XRD patterns of the three forms were again determined by Fronczek *et al.* [5] at 100 K. The results indicate that the parameters in Table 1 are accurate for each of the mannitol polymorph.

Even though different nomenclatures have been used in various literatures for mannitol polymorphs or their mixtures, such as C and D in Giron's work [33] or γ in Rye's work [22] (all should be mixtures), the summarization based on the crystal structural parameters in this paper should provide a clear perspective for the polymorphism of mannitol.

3. Crystal Growth Kinetics of Mannitol Polymorphs

The crystal growth process is difficult to follow for polymorphic material due to the potential transformation tendency as mentioned before. As in mannitol polymorphs, limited researches have been reported on the growth kinetics in different crystallization processes.

Nakagawa *et al.* [34] studied the crystal behavior of mannitol polymorphs in a freezing solution, and found that the amount of each polymorph was correlated to the ice crystal nucleation temperature and the cooling rate. To elucidate the results, they did a qualitative estimation to the crystal growth at the liquid–solid interface. Even though it was reasonable to believe that the cooling rate could influence both the polymorphic transition and crystal growth and then cause the amount difference of various polymorphs along the freezing-dried cake, it didn't provide detailed growth kinetics to each polymorphs. In another freeze-drying process, Liao *et al.* [35] found that annealing could facilitate both mannitol nucleation and crystal growth even when a crystallization inhibitor, an active pharmaceutical ingredient, was present. Similarly, Dixon *et al.* [36] investigated the influence of protein on the polymorphism of mannitol during lyophilization, and the results illustrated that more δ and less β mannitol were produced when the protein concentration increased from 1 to 5 $\text{mg}\cdot\text{mL}^{-1}$. But as the protein

Table 1

The review of unit cell parameters and nomenclature of D-mannitol anhydrous polymorphs in literatures

Mark	Literature	Space group	a/nm	b/nm	c/nm	$\beta/(^\circ)$	v/nm ³	z	$D_x/\text{kg}\cdot\text{m}^{-3}$
β	Marwick, 1931 [21]	$\text{P2}_1\text{2}_1\text{2}_1$	0.865	1.690	0.556	–	203 ^①	4	1.488
β	Rye, 1952 ^② [22]	$\text{P2}_1\text{2}_1\text{2}_1$	0.865	1.690	0.556	–	203 ^①	4	1.488
β	Berman, 1968 [23]	$\text{P2}_1\text{2}_1\text{2}_1$	0.8672	1.6875	0.5560	–	–	4	1.487
β	Walter-Levy, 1968 [4]	$\text{P2}_1\text{2}_1\text{2}_1$	0.8672	1.689	0.5549	–	–	4	1.489
β	Kaminsky, 1997 [24]	$\text{P2}_1\text{2}_1\text{2}_1$	0.8694 (7)	1.6902 (8)	0.5549 (6)	–	815	4	1.490 (2)
β	R. Fronczek, 2003 [5]	$\text{P2}_1\text{2}_1\text{2}_1$	0.55381 (10)	0.8580 (2)	1.6795 (5)	–	789.0 (3)	4	1.516
α	Walter-Levy, 1968 [4]	$\text{P2}_1\text{2}_1\text{2}_1$	0.8839	1.8778	0.4896	–	–	4	1.470
K	Kim, 1968 [25]	$\text{P2}_1\text{2}_1\text{2}_1$	0.8942	1.8798	0.4893	–	–	4	1.471
α	R. Fronczek, 2003 [5]	$\text{P2}_1\text{2}_1\text{2}_1$	0.48653 (10)	0.8873 (2)	1.8739 (3)	–	809.0 (3)	4	1.496
δ	Walter-Levy, 1968 [4]	P2_1 or $\text{P2}_1/\text{m}$	0.5095	1.8254	0.4919	118.36	–	2	1.501
δ	R. Fronczek, 2003 [5]	P2_1	0.4899 (2)	1.8268 (6)	0.5043 (2)	118.39 (2)	397.0 (3)	2	1.524
δ	Botez, 2003 [26]	P2_1	0.508941 (5)	1.82504 (2)	0.491702 (5)	118.303	402.103	2	1.377 ^③

^① Volume per molecule, and others are volume per unit cell.

^② The author also mentioned that the β form they obtained was in agreement with Marwick's result.

^③ The densities of mannitol polymorphs in this work are all lower than others (1.394 $\text{kg}\cdot\text{m}^{-3}$ for the β form).

concentration was above $10 \text{ mg} \cdot \text{ml}^{-1}$, the nucleation and growth of all mannitol forms were inhibited.

In addition to freezing experiments, the crystallization mechanism of mannitol in a microdroplet evaporation was discussed by Poornachary *et al.* [37], where the growth rate along the needle axis was firstly identified as $(1.5 \pm 0.2) \mu\text{m} \cdot \text{s}^{-1}$ and $(0.3 \pm 0.1) \mu\text{m} \cdot \text{s}^{-1}$ for the δ and β forms, respectively. Typically the faster growth rate was considered the reason to cause the appearance of the δ mannitol in the solution–substrate contact line where the local supersaturation was usually high due to the Marangni-driven convection. Moreover, while focusing on the nano-crystalline cluster of mannitol, Hammond *et al.* [38] found that the conformational variability was higher for the stable β form in the early stages of crystal growth compared to the metastable δ form.

In bulk aqueous solution, the solvent-mediated polymorphic transformation is quite obvious for mannitol metastable forms [39,40] especially when the temperature is not low, which makes it even more difficult to clarify the growth mechanism. Crisp *et al.* [41] reported that the growth of mannitol polymorphs could be affected by the preferred orientation effects, thus the amount of δ form increased with the content of the antisolvent (e.g. acetone) during crystallization. In another study, Cornel *et al.* [8] used the growth rates of these mannitol polymorphs for a transformation model, but the parameters were only selected qualitatively to satisfy the nucleation experiments without any precise calculation. Additionally, O'Sullivan *et al.* [40] detected the growth of the metastable δ form clearly by focused beam reflectance measurement (FBRM) in a polymorphic transformation process, but unfortunately the kinetics were not confirmed. According to the literatures, it is obvious that the growth kinetics of mannitol, especially of the metastable forms, haven't been investigated clearly even though bulk crystallization is quite common in industry to produce mannitol polymorphs. Thus in order to enlarge the acquaintance to the growth of δ mannitol, the induction time measured in our previous work [42] was reanalyzed here to provide the growth mechanism following a reported method by Kuldiplumar *et al.* [20].

4. Crystal Growth Mechanism of δ Mannitol by Induction Time Measurement

4.1. Theory

Generally the induction time can be considered as being made up of several parts, such as [43] the times for the system to achieve a quasi-steady state distribution of molecular clusters, for the formation of a stable nucleus, and for the nucleus to grow to a detectable size. Thus it is related to the rates of both nucleation and growth of crystals:

$$t_{\text{ind}} = \frac{1}{JV} + \left(\frac{\alpha}{a_n J G^{n-1}} \right)^{1/n} \quad (1)$$

where J is the rate of nucleation, V is the volume of the system, α is the volume fraction of the new formed phase, G is the rate of crystal growth, a_n is a factor related to the crystal shape with $n = m\nu + 1$ (m indicates the dimensionality of growth while ν equals 0.5 or 1 depending on the crystal growth is controlled by volume diffusion or surface reaction, respectively). Generally the first term is usually negligible compared to the second especially when the supersaturation is not too low as in our case, which leaves Eq. (1) to the following:

$$t_{\text{ind}} = \left(\frac{\alpha}{a_n J G^{n-1}} \right)^{1/n} \quad (2)$$

In this scenario, the steady state nucleation rate is usually described as below:

$$J = K_J s \cdot \exp\left(-\frac{B}{\ln^2 s}\right), \quad B = \frac{4f_s^3 \gamma^3 \nu^2}{27f_v^2 k^3 T^3} \quad (3)$$

where s is the supersaturation, K_J is the nucleation rate constant, and B is a constant composed of the shaper factors (f_s , the surface shape factor, and f_v , the volume shape factor), molecular volume (ν), and the interfacial free energy (γ).

The dependence of growth rate on supersaturation can be expressed as:

$$G = K_G f(s) \quad (4)$$

where K_G is the growth rate constant and $f(s)$ is a function of supersaturation depending on specific growth mechanism. Combining Eqs. (2), (3) and (4), it can be obtained:

$$t_{\text{ind}}(s) = A_p [f(s)]^{(1-n)/n} \cdot s^{-1/n} \cdot \exp\left(\frac{B}{n \ln^2 s}\right), \quad A_p = \left(\frac{\alpha}{a_n K_J K_G^{n-1}}\right)^{1/n} \quad (5)$$

It is clear that the induction time (t_{ind}) and supersaturation (s) can be related to Eq. (5) once the crystal growth mechanism is fixed. Generally there are four kinds of growth mechanisms $f(s)$ in the literature [20] as listed in Table 2.

Since the δ form of mannitol is thin rod like [39], the dimensionality of growth is set to $m = 1$. In the normal growth mechanism, the spiral growth mechanism, and the 2D nucleation-mediated mechanism, the growth rate is technically determined by the surface reaction in a growth unit, thus $\nu = 1$ and the factor n is correspondingly 2 as displayed in Table 2. While the growth is controlled by the transport of growth units through the solution to the crystal surface as in the volume diffusion-controlled mechanism, one can accordingly get that $\nu = 0.5$ and n is 1.5 as shown in Table 2.

By introducing different $f(s)$ in Table 2 to Eq. (5), it is possible to relate the supersaturation and the induction time under different mechanisms [44]. To easily do this, another function $F(s)$ [20] was derived by rearranging Eq. (5) for normal, spiral, and volume diffusion-controlled growth:

$$F(s) \equiv \ln \left\{ s^{1/n} \cdot [f(s)]^{(n-1)/n} \cdot t_{\text{ind}} \right\} = \ln A_p + \frac{B}{n \ln^2 s} \quad (6)$$

According to Eq. (6) the relationship of $F(s)$ versus $1/(\ln^2 s)$ can be fitted by a straight line for various of n . Similarly for 2D nucleation-mediated growth, the function is defined as:

$$\begin{aligned} F(s) &\equiv \ln \left[(s-1)^{2(n-1)/3n} \cdot s^{(n+2)/3n} \cdot t_{\text{ind}} \right] \\ &= \ln A_u + (n-1) \frac{B_{2D}}{3n \ln s} + \frac{B}{n \ln^2 s} \end{aligned} \quad (7)$$

Thus the plot of $F(s)$ versus $1/(\ln s)$ can be fitted by a parabolic curve. Depending on the goodness of the fit to Eqs. (6) or (7), it should be identified the growth mechanism as one of the four above once the correlation index (R^2) is in the tolerant range. The expressions of $F(s)$ for different operating mechanisms are also shown in Table 2.

4.2. Results and discussion

The determination of induction time for metastable polymorph is difficult due to the transition tendency, that is why the *in situ* Raman spectroscopy and FBRM were combined to distinguish the polymorph and measure the induction time simultaneously in our previous work

Table 2
Functions and parameters for different crystal growth mechanisms

Growth mechanism	$f(s)$	ν	n	$F(s)$ based on Eqs. (6) or (7)
Normal growth	$f(s) = s - 1$	1	2	$F(s) = \ln[s^{1/2} \cdot (s-1)^{1/2} \cdot t_{\text{ind}}] = \ln A_p + \frac{B}{2\ln^2 s}$
Spiral growth	$f(s) = (s-1) \ln s$	1	2	$F(s) = \ln\{s^{1/2} \cdot [(s-1)\ln s]^{1/2} \cdot t_{\text{ind}}\} = \ln A_p + \frac{B}{2\ln^2 s}$
2D nucleation-mediated ^①	$f(s) = (s-1)^{2/3} \cdot s^{1/3} \cdot \exp(\frac{-B_{2D}}{3\ln s}), B_{2D} = \frac{\beta_{2D}\kappa^2 a}{(kT)^2}$	1	2	$F(s) = \ln[(s-1)^{1/3} \cdot s^{2/3} \cdot t_{\text{ind}}] = \ln A_u + \frac{B_{2D}}{6\ln s} + \frac{B}{2\ln^2 s}, B_{2D} = \frac{\beta_{2D}\kappa^2 a}{(kT)^2}$
Volume diffusion-controlled	$f(s) = s - 1$	0.5	1.5	$F(s) = \ln[s^{2/3} \cdot (s-1)^{1/3} \cdot t_{\text{ind}}] = \ln A_p + \frac{2B}{3\ln^2 s}$

^① β_{2D} is a numerical 2D shape factor, κ is the specific edge free energy of the nuclei, and a is the molecular area.

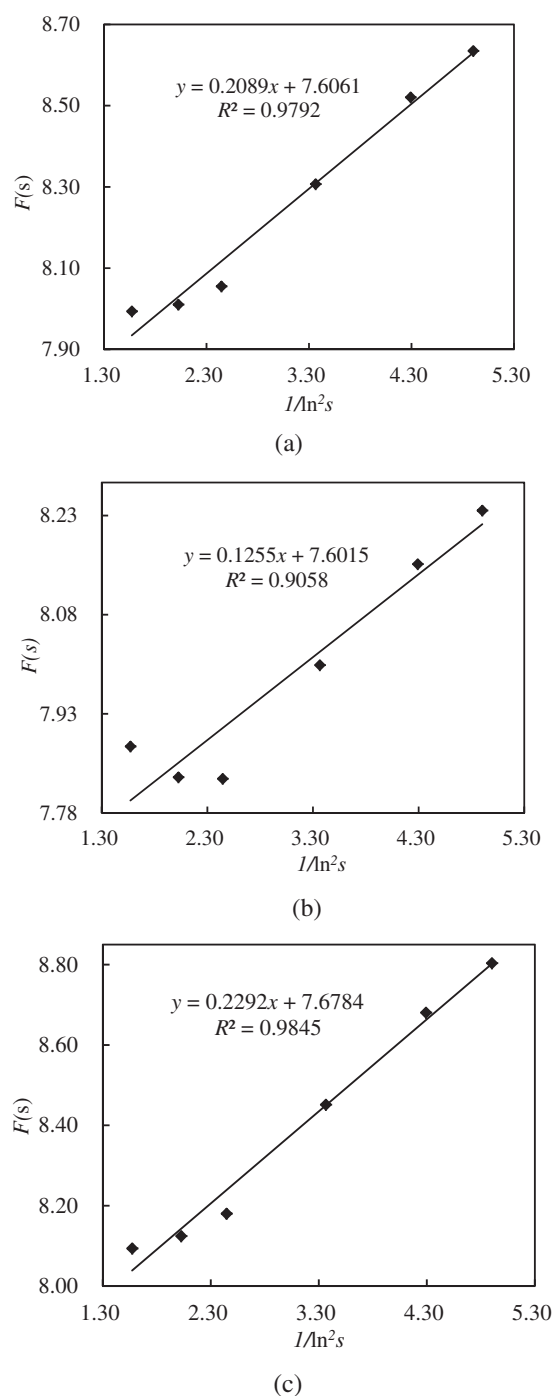


Fig. 2. Plots of $F(s)$ versus $1/\ln^2 s$ for δ form of mannitol under (a) the normal growth mechanism, (b) the spiral growth mechanism, (c) the volume diffusion controlled growth mechanism.

[42]. Here in this paper, the induction time and supersaturation data were reanalyzed in order to fulfill different growth mechanisms. Specifically the calculated $F(s)$ are plotted against $1/(\ln^2 s)$ for the normal, spiral, and volume diffusion-controlled growth mechanism as shown in Fig. 2, while $F(s)$ against $1/(\ln s)$ is plotted in Fig. 3 following the 2D nucleation-mediated growth mechanism.

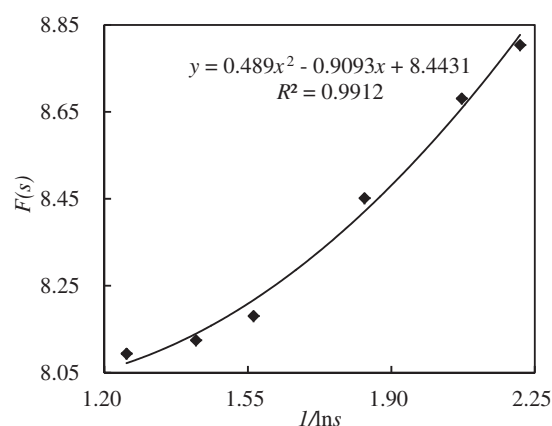


Fig. 3. Plot of $F(s)$ versus $1/\ln s$ for δ form of mannitol under the 2D nucleation-mediated growth mechanism.

It is clear that the three linear fittings in Fig. 2 are quite different. The correlation coefficient is as poor as 0.9058 in Fig. 2(b), which means that the growth of the δ form of mannitol is barely following the spiral growth mechanism. The data points in Fig. 2(a) are fitted to the normal growth mechanism while those in Fig. 2(c) are fitted to the volume diffusion controlled growth mechanism. It can be seen that the correlation coefficients of these two fittings are better than that in the spiral growth mechanism. But the largest R^2 of 0.9912 appears when the data are fitted to the 2D nucleation-mediated mechanism as shown in Fig. 3. Therefore it is reasonable to believe that the growth mechanism of the metastable δ form of mannitol should be 2D nucleation-mediated in a cooling crystallization. Since δ mannitol only nucleates at high initial concentration in aqueous solution as mentioned in our previous paper [42], it seems that once this metastable form nucleates from the solution, the growth is mediated by the formation and spread of numerous 2D nuclei.

The method used in this work for crystal growth mechanism investigation has only been used in material without polymorphism phenomenon in the literature [20,44]. However the high correlation index indicates that it should be suitable for polymorphic materials. To testify this, more detailed and microscopic work will be done in the future.

5. Conclusions

The nomenclature of D-mannitol polymorphs is summarized in this paper due to the confusion of polymorph identification. It was

confirmed that there are three pure anhydrous forms of mannitol based on the unit cell parameters even though some of them have been given various names in different literatures. The three pure mannitol polymorphs are named β , α , and δ in this work based on the review to many publications. Moreover the literatures on crystal growth of mannitol polymorphs are reviewed, and it was found the growth can kinetically be affected by many factors. After that, the induction time previously determined by us is applied to investigate the crystal growth mechanism of the δ mannitol polymorph of mannitol in a bulk crystallization. And it was found that the growth of the metastable δ form should be 2D nucleation-mediated.

Nomenclature

a	the molecular area, m^2
a_n	a factor related to the crystal shape in the expression of induction time
B	a constant related to the nucleation rate
D_x	crystal density, $\text{kg} \cdot \text{m}^{-3}$
f_s	the surface shape factor
f_v	the volume shape factor
G	rate of crystal growth, $\text{m} \cdot \text{s}^{-1}$
J	rate of nucleation, $\text{m}^{-3} \cdot \text{s}^{-1}$
K_G	growth rate constant, $\text{m} \cdot \text{s}^{-1}$
K_j	nucleation rate constant, $\text{m}^{-3} \cdot \text{s}^{-1}$
m	the dimensionality of growth
s	Supersaturation ($s = c/c^*$)
t_{ind}	induction time, s
V	system volume, m^3
v	molecular volume, m^3
α	volume fraction of the new formed phase
β_{2D}	a numerical 2D shape factor
γ	interfacial free energy, $\text{J} \cdot \text{m}^{-2}$
κ	specific edge free energy of the nuclei, $\text{J} \cdot \text{m}^{-2}$

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