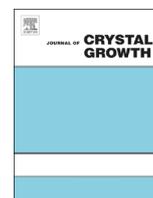




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Investigation of the L-Glutamic acid polymorphism: Comparison between stirred and stagnant conditions



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ABSTRACT

This work highlights the effect of the stirring, the temperature and the supersaturation on the cooling crystallization of L-Glutamic acid (LGlu) polymorphs. First, solubility measurements of the metastable polymorph α and the stable polymorph β were performed. Then, crystallization experiments were carried out in stirred vessel and in stagnant cell. All these experiments were monitored by *in situ* devices. The effect of the temperature on the LGlu polymorphs was found to be more relevant than the supersaturation in the stirred crystallizer. In the stagnant cell, only the stable form β crystallized regardless of the operating conditions. Moreover, an unexpected and new habit of the β form was discovered and confirmed. These results suggest that the temperature and the stirring can strongly affect the nucleation and the growth kinetics of polymorphic forms.

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1. Introduction

“When a substance can exist in more than one crystalline state it is said to exhibit polymorphism” [1]. Two polymorphs have the same chemical composition but different physical and chemical properties (solubility, compressibility, melting point...) and then are considered as two different materials [2]. Therefore, the ability to fully characterize all the polymorphs is of crucial importance particularly in the pharmaceutical industry. This is to avoid any transformation during manufacturing or storage and to crystallize the selected polymorph. However, this stays a challenge regarding the numerous of questions that remain still unresolved despite the high number of publication on this topic [3–5]. Amongst them, the order and/or the reason of appearance or disappearance of a polymorphic form but also how the polymorphic transition occurs can be cited. The ideal purpose of this work is to find general rules, bonding to all polymorphic systems, in order to answer these questions.

L-Glutamic acid (LGlu) is an amino acid widely used in pharmaceutical and food industry. This compound is known to exhibit monotropic polymorphism and to have two polymorphs: a stable one called β with needle like shape and a metastable one called α with prismatic shape [6]. Since the β form can generate many

difficulties in production, transport and storage, it is more suitable to produce the α form [1]. Many works have investigated the LGlu behavior in water in case of cooling crystallization. When high cooling rates were applied in stirred vessel, LGlu has been reported to form the α polymorph at low temperature whatever the supersaturation [6,7]. However, at higher temperature (45 °C) and depending on the supersaturation, only β form or both polymorphs α and β were observed [2,6,8]. Different results have been reported using other experimental setups [9,10]. For example, Ni et al. [10] have studied the effect of supersaturation and cooling rate on the nucleation of each LGlu polymorph in an oscillatory baffled crystallizer; the authors have noticed that independently of the cooling rate, it is more likely to produce the α form at low supersaturations and the β form at high supersaturations. Polymorphic transition from the α LGlu to the β LGlu has also been investigated and identified as a solvent-mediated transition with low rates at low temperatures [2,6,11,12]. Considered as a model compound [5,13], L-Glutamic acid does not appear as well-known as it seems. Hence, numerous questions remain with unsatisfactory answers. For instance, questions regarding the key parameters controlling the crystallization of each polymorph and the obedience of the LGlu to the Ostwald rule of stages; but also, the influence of the stirring on the crystallization of the LGlu.

The aim of this work is to clarify how the nucleation and the growth of a polymorph of a model compound can be affected by supersaturation ratio, temperature and stirring. The L-Glutamic acid is selected to answer these questions. The influences of the initial and final temperatures and of the supersaturation ratio are

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investigated in stirred and stagnant conditions. In stirred conditions, the effect of these parameters on the nucleation and the crystal growth is evaluated *in situ* thanks to a video probe and a FBRM probe while the concentration of the LGlu is measured offline by a gravimetric method. In stagnant conditions, the different events are observed in a thermostated cell with a microscope. The results discussed below allow better understanding of the L-Glutamic acid polymorphism and more generally polymorphism.

2. Experimental section

2.1. Materials

L-Glutamic acid, supplied by Sigma Aldrich Co. Ltd. (Lot BCBH3883V, chemical purity $\geq 99.5\%$), and ultrapure water were used in the experiments presented hereafter.

Firstly, the commercial LGlu was analyzed by X-ray powder diffraction which confirmed the presence of the only stable polymorph β . Secondly, the α polymorph was obtained by cooling an aqueous solution of LGlu with a concentration of 15 g/kg of solvent, from 50 °C to 5 °C with a cooling rate of -1.5 °C/min. Fifty minutes of waiting at 5 °C were required to mainly nucleate the α polymorph. The α form crystals were then quickly filtrated and dried at room temperature before being analyzed by X-ray powder diffraction and Scanning Electron Microscopy (SEM). The results obtained are reported on Fig. 1. In both cases, the XRD pattern exhibits the presence of only one polymorph.

The SEM analyses were performed with a FEI Quanta 250 FEG microscope. The powder was dropped off on a flat steel holder before being coated under vacuum by cathodic sputtering with copper (20 nm). Then, the sample was observed under an accelerating voltage of 15 kV.

2.2. Solubility measurement

A stirred double jacketed glass vessel of 100 mL was used to determine the solubility of the polymorphs α and β in pure water. The temperature of the slurry was controlled by heating/cooling bath circulation thermostat (ministat230, Huber[®], Germany) and

checked by a calibrated temperature sensor (T900, Dostmann electronic GmbH[®], Germany) with ± 0.03 °C accuracy. The reactor was equipped with a condenser cooled with cold water to avoid any solvent loss by evaporation, and a 3-blade glass stirrer.

First of all, the time required for the solution to reach thermodynamic equilibrium has to be determined. Preliminary kinetic experiments were performed to assess this time. The lowest temperature of 10 °C was chosen, since it should be at this temperature that the kinetics is the lowest. Thus, an excess of solid was added to the solution kept at 10 °C. Then, two solution samples were withdrawn from the crystallizer every hour by means of a two milliliters pipet equipped with a filter. All the samples were then kept at 85 °C for 24 h in a ventilated oven to remove all the water. The samples were weighted before and after the evaporation, at room temperature, using an analytical balance (CP225D, Sartorius, France) with ± 0.01 mg accuracy, and the concentrations of LGlu were deduced.

The evolution of the concentration with time is presented in Fig. 2 for both polymorphs. The results show that a minimum of two hours was required to reach solid/liquid equilibrium. This duration of two hours was chosen to measure the solubility of the two polymorphs between 10 °C and 70 °C following the same gravimetric method as detailed above.

In the case of the α LGlu solubility measurement, the *in situ* video probe (described in Section 2.3.1), allowed to check that the polymorphic transition did not occur at the considered temperatures. It is worth noting that the concentration remains at the solubility of the α form as long as the α crystals are present in solution [8,14].

In order to determine the error of the measurement, 10 samples were removed at the same temperature and analyzed. The estimate of standard deviation was divided by the square root of the samples number, then the result was multiplied by 2.26 corresponding to a confidence level of 95%. The error deduced was $\pm 1.48\%$.

2.3. Crystallization experimental setups and operating conditions

2.3.1. In stirred conditions

2.3.1.1. *Experimental setup.* The batch cooling crystallization experiments were carried out in a 2 L double jacketed glass vessel

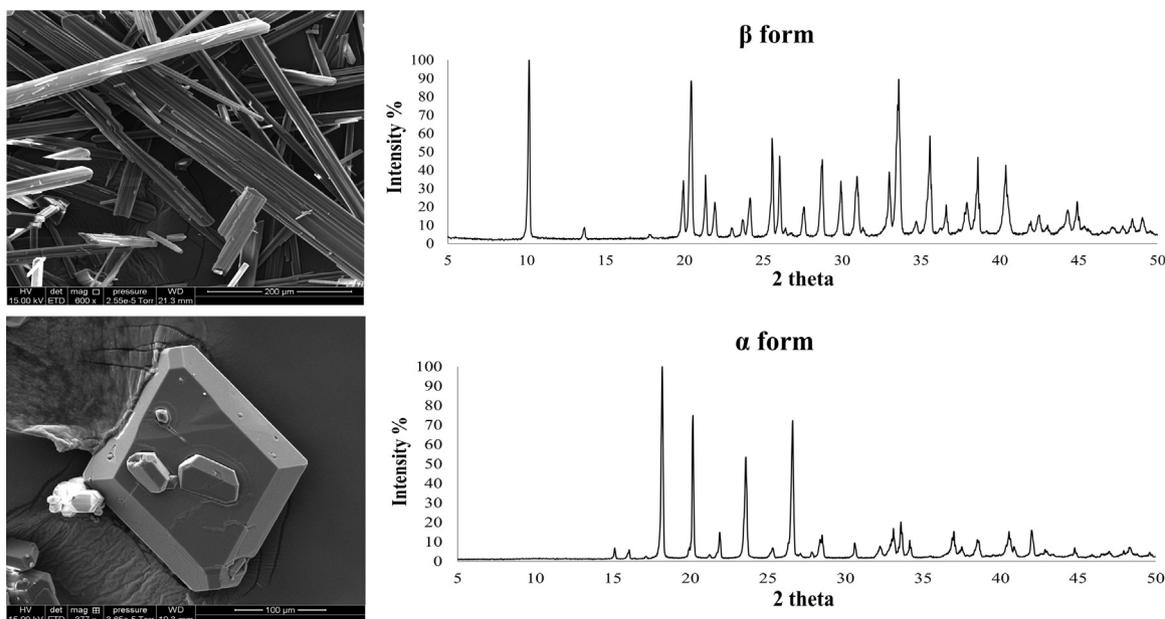


Fig. 1. SEM micrographs and XRD patterns of the stable β and the metastable α polymorph of L-Glutamic acid.

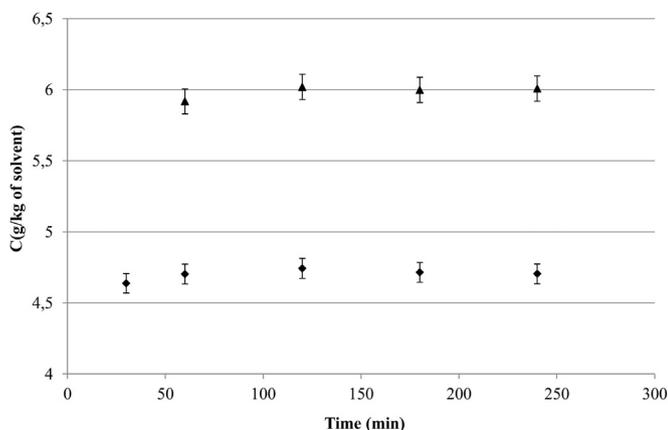


Fig. 2. Equilibrium study of each polymorph of LGlu at 10 °C: ♦ the β form, ▲ the α form.

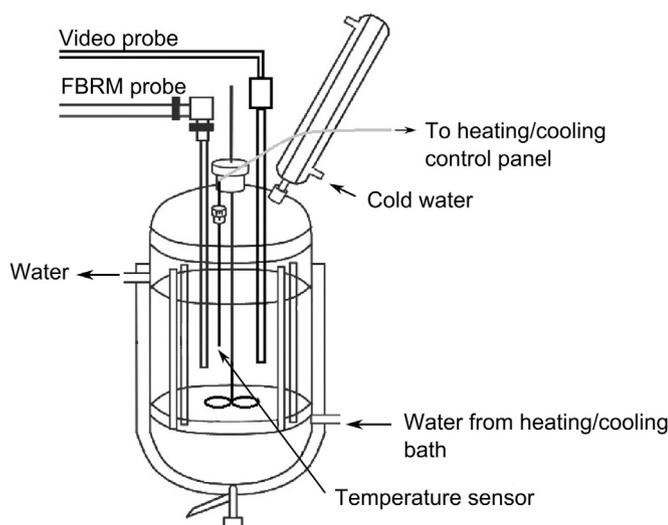


Fig. 3. Experimental batch cooling crystallization setup equipped with *in situ* sensors.

with an inner diameter of 150 mm (cf. Fig. 3). The reactor was equipped with a condenser cooled with cold water. Four stainless steel baffles associated with a speed controlled mechanical stirrer, composed of a 3-blade stainless steel profiled propeller (TT Propeller, Mixel[®], France) placed at 50 mm above the bottom of the reactor, were used to ensure the homogeneity of the mixing. For all the experiments, the stirring rate was set at 300 rpm to promote a turbulent state. The temperature of the suspension was measured continuously by a Pt100 probe, and controlled by manipulating the set point temperature of the heating/cooling bath circulation thermostat (CC231, Huber[®], Germany).

Two probes were immersed in the crystallizer for *in situ* monitoring: the first one is a video probe, developed in our laboratory [15] (EZProbe[®] 12005), allowing to observe the nucleation of the polymorphic form and how it evolved. The second one is a Focused Beam Reflectance Measurement probe (FBRM D600L, Lasentec[®], Redmond, USA) that provided particle count numbers in real time and the temporal evolution of the chord-length distributions (CLDs). In this study, the CLDs were collected with a laser speed of 2 m/s and a measurement duration of 2 s. The FBRM probe gave the CLDs even at high solid concentration and allowed a reliable detection of the nucleation.

The concentration of LGlu in the solution, during the crystallization, was measured with the same gravimetric method described above (cf. Section 2.2). The error value, $\pm 0.30\%$, was

Table 1
Operating conditions in the stirred crystallizer.

LGlu initial concentration (g/kg of solvent)	Equilibrium temperature of the β form (°C)	Supersaturation ratio (calculated regarding β form), S_{β} (–)	Final temperature (°C)
43	72	1.5; 3.0	60; 40; 10
31	61	1.7; 4.2	45; 10
22	51	1.7; 2.2; 6.1	35; 30; 5
15	40	1.8; 2.8; 4.2	25; 15; 5

also determined with the same statistical method described earlier.

2.3.1.2. *Operating conditions.* The effect of the supersaturation and the temperature on the crystallization of the stable polymorph β and the metastable polymorph α was investigated in a stirred batch crystallizer. The initial concentrations, the equilibrium temperatures, the final temperatures and the supersaturation ratios regarding the β form solubility at the nucleation point (calculated regarding the β form solubility) are shown in Table 1. The cooling was kept at -1.5 °C/min and was always started 10 °C above the corresponding equilibrium temperature. Instantaneous information about when and which polymorphic form nucleated were given by the *in situ* video and FBRM probes. All the experiments were pursued several hours after the nucleation event.

2.3.2. In stagnant conditions

2.3.2.1. *Experimental setup.* Non-agitated cell of 4 mL was used in all the stagnant experiments (cf. Fig. 4a). The temperature of the cell was controlled by Peltier elements (Anacrismat[®], France) (cf. Fig. 4b). The whole setup was placed under a microscope (DMI3000 B, Leica[®], Germany) equipped with a camera (DFK21BF04, The Imaging Source[®], Germany). The camera took pictures of the crystals every 10 s. The Peltier elements could be moved to place the focus of the camera at any spot of the cell. The Peltier elements temperature was controlled and recorded by software that also allowed image recording. It is worth noting that the temperature of the slurry was not measured but was assumed to be very close to the Peltier elements temperature.

2.3.2.2. *Operating conditions.* Solutions at different concentrations were prepared in the 4 mL cell then cooled to different temperatures (-1.5 °C/min). All the operating conditions are reported in Table 2. Low supersaturation ratios similar to those applied in the stirred vessel ($S_{\beta}=1.5; 1.7; 2.2$) were also investigated; however, the spontaneous nucleation of LGlu was never observed because the induction times were very long (more than 72 h).

3. Results and discussion

3.1. Solubility curves

The solubility of the α and the β polymorphic forms of L-Glutamic acid in pure water were investigated according to the experimental protocol described previously. The aim here was to validate the experimental protocol and obtain fundamental data in order to characterize our system.

The results reached are depicted in Fig. 5 and compared with the data available in the literature [14,16]; a good agreement is obtained. As it can be clearly seen in Fig. 5, the solubility of the α polymorph is higher than the solubility of the β polymorph, confirming that the L-Glutamic acid is a monotropic system between

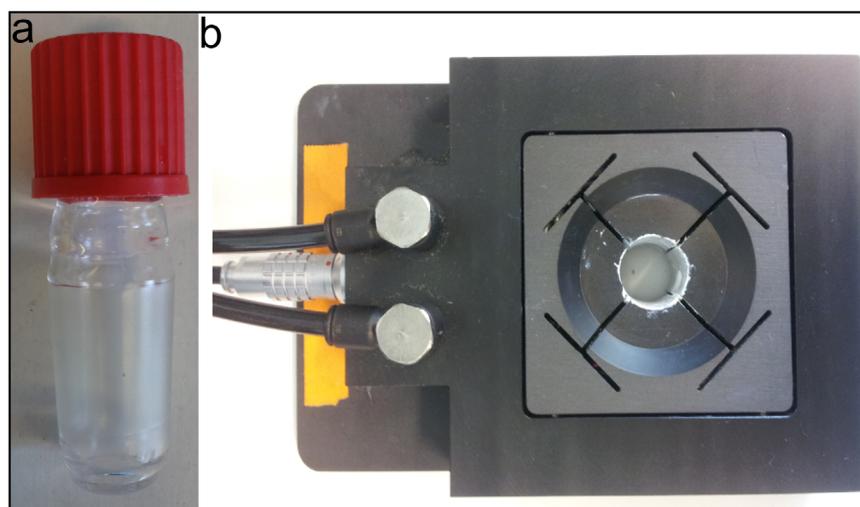


Fig. 4. Experimental setup in stagnant conditions: (a) 4 mL cell, (b) Peltier elements.

Table 2
Operating conditions in the stagnant cell.

LGlu initial concentration (g/kg of solvent)	Equilibrium temperature of the β form ($^{\circ}\text{C}$)	supersaturation ratios (calculated regarding β form), S_{β} (-)	Final temperature ($^{\circ}\text{C}$)
43	72	3.0; 6.3; 9.0	40; 20; 10
31	61	4.5; 6.5	10; 20
26	57	4.5; 5.5	10; 15
22	51	4.6	10

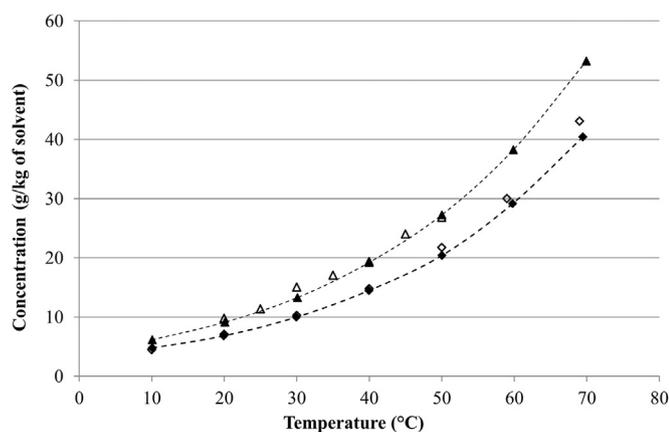


Fig. 5. Solubility curves of the polymorphic forms of L-Glutamic acid in pure water. \blacklozenge and \blacklozenge depict the solubility data obtained in this work respectively for the stable polymorph β and the metastable polymorph α . For comparison, the solubility data reported by Manzurolo et al. [16], for the β form, and Mo et al. [14], for the α form, are reproduced respectively as \blacklozenge and \blacktriangle .

10 $^{\circ}\text{C}$ and 70 $^{\circ}\text{C}$ in which α is the metastable form and β is the stable form.

However, in order to check that no undetected issues have taken place during the experiment, the Van't Hoff equation is plotted, i.e. the natural logarithm of the solubility (expressed in molar fraction) as a function of $1/T$ (Temperature, K). Fig. 6 presents the plots obtained in this work together with those reported in the literature [14,16].

Fig. 6 clearly shows the very good linearity of the curves obtained in this work, which tends to validate the solubility curves obtained. It has to be noted that the linear fitting of our

data is, again, in a good agreement with those reported in the literature.

3.2. Crystallization experiments performed in stirred conditions

Experiments were performed in the 2 L double jacketed glass vessel presented above. The aim was to determine the zone of spontaneous nucleation but also to understand the order of apparition and the repartition between the two polymorphic forms of LGu regarding the supersaturation ratio (S_{β}) and the nucleation temperature. Indeed, in this work, the S_{β} was ranging between 1.5 and 6.1, while the nucleation temperature was varying between 5 and 60 $^{\circ}\text{C}$. The results obtained are reported in Fig. 7 and are accompanied by several video pictures of the crystals; these pictures were taken 75 min after the nucleation event. The solubility curves of the α and the β forms are also represented.

It is worth noting that Fig. 7 shows several shapes markers that inform about the temperature at which the nucleation event was detected by the FBRM probe but also about the polymorphic form appearing first and the nature of the predominant one. The experiments were labeled from (a) to (j) in order to facilitate the discussion. Hence, experiments labeled (a), (c), (e) and (h) were performed at low S_{β} , between 1.5 and 1.8; while the experiments (b), (d) and (g) were carried out at high S_{β} , ranging from 3.0 to 6.1. Each point corresponds to a single and different experiment except for point (b). For example, regarding experiment (c), the initial concentration was equal to 31 g/kg of solvent and the cooling was conducted from 71 $^{\circ}\text{C}$ (10 $^{\circ}\text{C}$ above the equilibrium temperature, see Table 1) to 45 $^{\circ}\text{C}$. The nucleation occurred 50 min after the final temperature of 45 $^{\circ}\text{C}$ was reached. Thus, point (c) represents the supersaturation and the temperature at which the nucleation took place. Obviously, the concentration in the solution started to decrease after the nucleation. For point (d), the cooling was started at the same initial conditions of concentration and temperature as those of point (c) but the cooling was pursued until 10 $^{\circ}\text{C}$. In that case, the nucleation occurred spontaneously at 22 $^{\circ}\text{C}$ which is represented by point (d) on Fig. 7. Points (a), (e)–(j) follow the same logic. As concern point (b), it represents two different experiments that have the same initial conditions but different final temperatures (40 $^{\circ}\text{C}$ and 10 $^{\circ}\text{C}$, see Table 1). Since the nucleation occurred at the same temperature of 40 $^{\circ}\text{C}$, which corresponds to the metastable zone limit for both runs, the two runs are represented by the same point (b).

Fig. 7 shows that the temperature has a significant influence on the appearance of a polymorphic form rather than the other. This

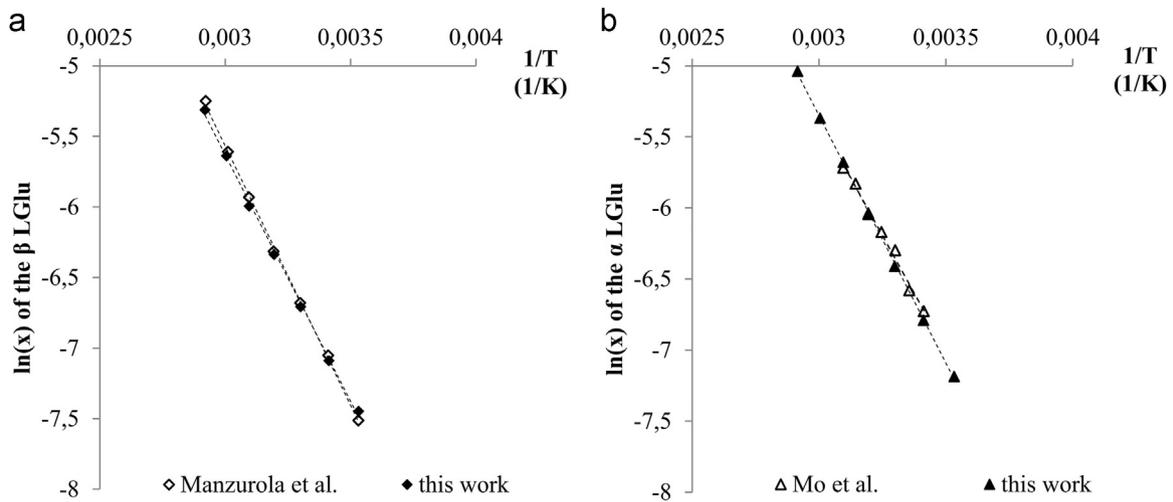


Fig. 6. Comparison of the Van't Hoff equation: (a) For the β polymorph: $\blacklozenge \ln(x) = -3494, 4/T + 4, 85$ ($R^2 = 0,9984$), $\diamond \ln(x) = -3674, 7/T + 5, 45$ ($R^2 = 0,9990$). (b) For the α polymorph: $\blacktriangle \ln(x) = -3485, 7/T + 5, 10$ ($R^2 = 0,9997$), $\triangle \ln(x) = -3235/T + 4, 31$ ($R^2 = 0,9909$).

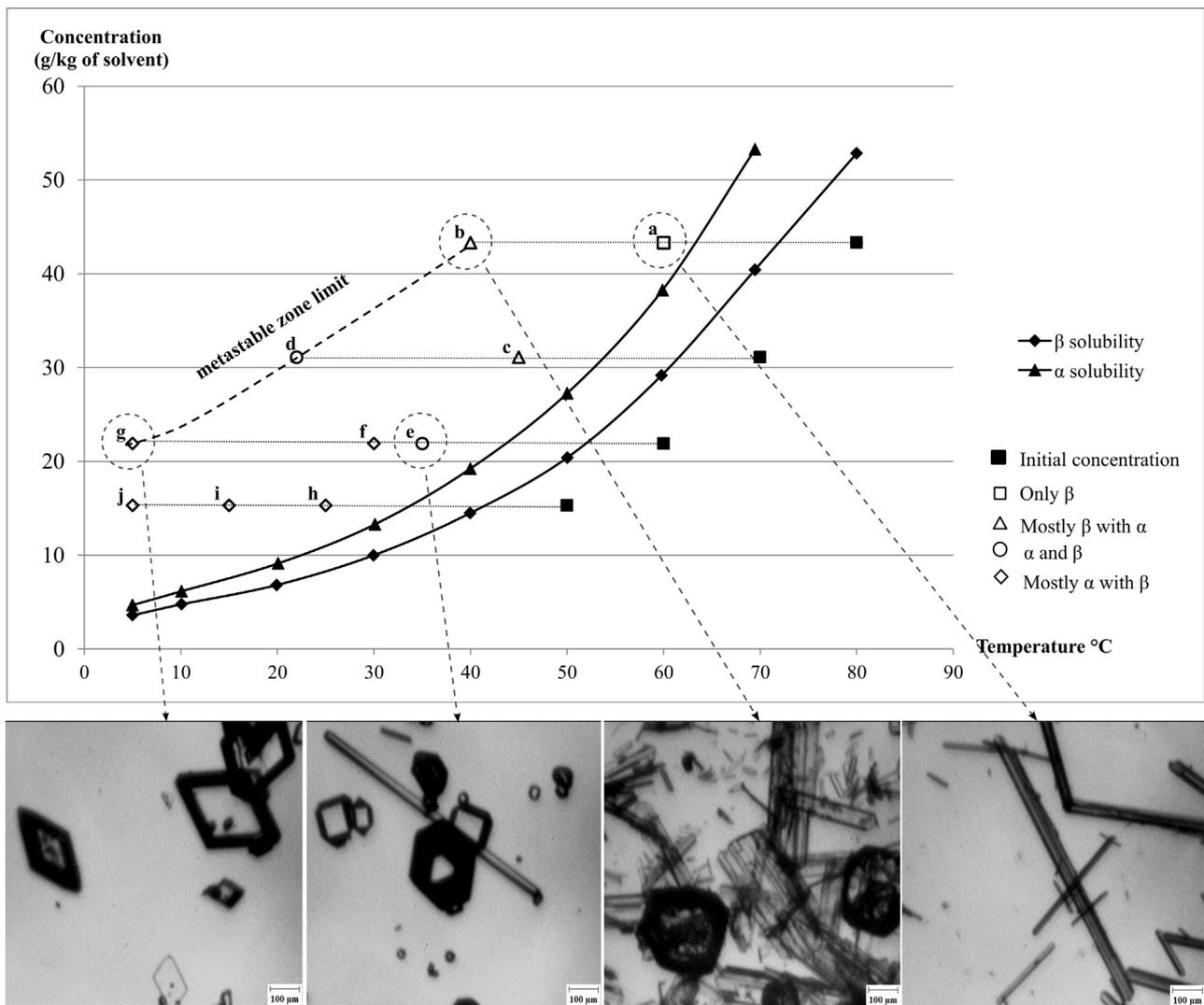


Fig. 7. Crystallization domains of α and β polymorphs.

observation, already reported by few authors [6,17], was not quantified until now. Thus, the α crystal fraction, at low supersaturation, increases from 0% (no detection by the video probe and

the XRD analysis) at high temperature ($60^{\circ}C$) to more than 99% (no detection of the β crystals by XRD analysis but few crystals were seen with the video probe) at ambient temperature ($25^{\circ}C$).

At high supersaturation, both polymorphs were crystallized with a high percentage of α at low temperatures (experiment (d) and (g)) and high percentage of β at higher temperature, (experiment (b)). These observations are in good agreement with the literature findings [6,17] which have stated that the α nucleation rate decreases with the increase of the temperature.

Moreover, experiments (b), (d) and (g) correspond to experiments for which, spontaneous nucleation of both polymorphs has been observed. They define the metastable zone limit for primary nucleation. However, the metastable zone specific of each polymorph could not be distinguished because the nucleation of the two polymorphic forms occurred in these three experiments.

As mentioned earlier, to follow the evolution of the suspension, all the experiments were carried on for several hours after the nucleation. In the experiments (b) and (c), the polymorphic transition were completed in 6 h. The α crystals took more than three days to vanish in the experiments (d) and (e) and more than 6 days in the experiments (f)–(j).

Studies on the nucleation kinetics of both polymorphs have shown that the relative nucleation rate of α (i.e. the ratio between α nucleation rate and the sum of α and β nucleation rates) decreased when the temperature increased [6] and that the effect of the temperature on the occurrence of the α form was more relevant than the supersaturation [17]. It has also been reported that the growth rate of the α crystals was higher than that of the β crystals [18]. Besides, the growth rate of the α form was logically found to increase with the temperature and the supersaturation [19]. Other works, which focused on the solvent-mediated transition from α to β , have stated that the polymorphic transition was very slow at low temperature even with the presence of the stable form β and that the transition kinetics strongly increased at high temperature [3,4,7]. This suggests that the β polymorph growth rate may be very slow at low temperature, even with a high

supersaturation.

These observations are in agreement with our results. Indeed, the key parameter in the LGlu polymorphs crystallization seems to be the temperature. At low temperature, since the α polymorph nucleation and growth were much faster, preferential crystallization of α was observed. This behavior follows the Ostwald rule of stages. At high temperature, the nucleation rate of the α form is slow and the growth rate of the β form is important, this may justify the predominance of the β form. These results suggest that LGlu polymorphism does not obey to the Ostwald rule of stages in the whole studied temperature domain.

3.3. Comparison with the results obtained in stagnant conditions

The cooling rate applied in stagnant conditions was the same than in stirred conditions, i.e. $-1.5\text{ }^\circ\text{C}/\text{min}$, and similar operating conditions were applied. Thus, the supersaturation ratios were varying between 3.0 and 9.0, and the final temperature between $10\text{ }^\circ\text{C}$ and $40\text{ }^\circ\text{C}$.

The first significant distinction between the stirred conditions and the stagnant conditions comes from the nucleation of the α polymorphic form of the L-Glutamic acid that was never observed in the 4 mL cells whatever the operating conditions of the experiment. Hence, only the β polymorphic form crystallized.

In order to compare the stagnant and the stirred operating mode, the same experiment was achieved in both the 2 L double jacketed glass vessel and the 4 mL cell ($S_\beta=6.5$; final temperature= $10\text{ }^\circ\text{C}$). The results obtained highlight the dissimilarity between the two reactors. Hence, the metastable form α has significantly nucleated in the stirred vessel while not a single α crystal was observed in the non-agitated cell. The dissimilarity was assumed to be caused by the high surface to volume ratio of the

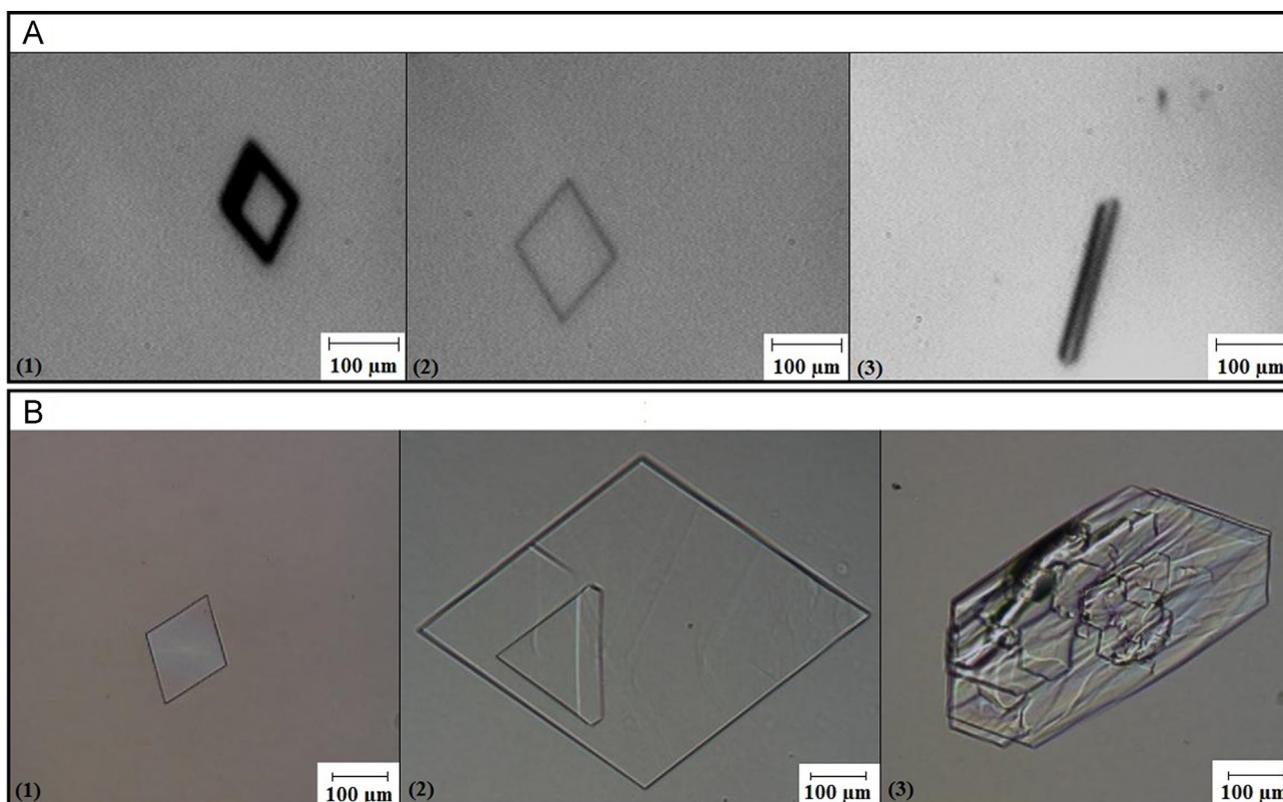


Fig. 8. *In situ* images of the LGlu polymorphs. A – In stirred conditions: (1) α form, (2) β form with lozenge-like shape ($S_\beta \geq 4$) and (3) β form with needle-like shape ($S_\beta < 4$). B – In stagnant conditions: (1) a β crystal ($3 \leq S_\beta \leq 9$), (2) the growth of a crystal for $S_\beta \geq 9$ and (3) the growth of a crystal for $S_\beta < 9$.

4 mL cell compared to the 2 L crystallizer which could favor the nucleation of the stable form, or by the weak mass transfer which could inhibited the α polymorphic form nucleation.

3.4. Unexpected result

It is commonly accepted that the α polymorph of L-Glutamic acid exhibits lozenge-like habit while the β polymorph exhibits needle-like habit.

However, the experiments performed at different supersaturation ratios allowed to observe a change in the crystal habit of the β polymorph. In stirred conditions, a needle-like shape was observed when the S_{β} was lower than 4 which is in agreement with the observations reported in the literature [20]. However, experiments carried out at supersaturation ratios higher than 4 have led to a different habit: a lozenge slab habit which is far away from the usual needle shape. Because of this habit close to that of α polymorph, it was first assumed to be the α polymorph. The hypothesis was forgotten after the isolation of the crystals and their analyses by X-ray Diffraction which concluded to the presence of the β polymorph alone. It is worth noting that the crystals with the new habit were quickly isolated after the nucleation and that they were not grinded before the XRD analysis to avoid any polymorphic transition. The different habits of the β polymorph and the habit of the α polymorph, in stirred conditions, are summarized in Fig. 8A.

These new results were confirmed in stagnant conditions. The β polymorph exhibited a lozenge slab as crystal habit and not a needle-like habit. The lozenge slabs grew with the same shape if the supersaturation ratio stayed higher than 9.0 or transformed to hexagonal slabs at supersaturation ratio lower than 9.0. The different habits obtained are summarized in Fig. 8B.

Therefore, relying only on the crystal appearance to differentiate between the two LGlu polymorphs can be misleading [21]. X-ray diffraction analysis is absolutely required to characterise the polymorph.

Hence, if the temperature was the most significant parameter to favor the crystallization of a polymorphic form rather than the other, the supersaturation ratio governs the crystals habit.

4. Conclusion

The effect of temperature and supersaturation on the crystallization of the L-Glutamic acid polymorphs in stirred and stagnant conditions was investigated. Spontaneous nucleation of both polymorphs (the stable β and the metastable α) was observed in the stirred conditions, with a preferential crystallization of the metastable form α at low temperatures and a predominance of the stable form β at high temperatures. Low nucleation and growth rates of the β crystals at low temperature could justify this behavior. Thus, the temperature seems to govern the crystallization of the LGlu polymorphs. In the stagnant conditions, only β crystals were observed even when the same operating conditions as in the stirred vessel were applied. The absence of the α crystals may be caused by the weak mass transfer or by the high surface to volume ratio in the stagnant cell. Finally, an unexpected habit change of the β crystals was reported for the first time. These results will be used to model and better understand the competition between nucleation and growth of the two polymorphic phases.

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