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The role of the intermediate stage of drying on particle in-situ crystallization in spray dryers

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**Abstract**

In-situ crystallization of particles in spray drying has several advantages particularly for product quality modification in the pharmaceutical industry. This process was investigated in a counter current spray dryer using lactose as a model material by manipulation of the local humidity within the drying chamber. Sample collection and humidity injection at different location of the dryer were carried out to better understand the mechanism of particle formation and solidification which are essential components of in-situ crystallization. They revealed that particle formation can be delayed by local humidity elevation. Differential scanning calorimetry and XRD of the yields showed that humidity manipulation was capable to produce semi crystalline lactose of up to 90 percent crystallinity. The results confirmed that there is a critical period for crystallization such that extending this period would significantly increase the degree of crystallization. Comparison on different requirements of crystallization indicated that extending the time for nucleation and the growth at the critical period via humidity manipulation has the most significant effect on the in-situ crystallization process.

**Keywords**: crystallization, counter current spray drying, lactose, humidity
1.0 Introduction

The control of particle crystallinity of pharmaceutical sugars through the spray drying process has recently attracted significant attention [1]. The process involves atomization of drug formulation into very fine droplets and then drying the droplet with hot air to form solid particles. During the solidification process, the initially dissolved solids in the droplet may solidify into a crystalline particle or rapidly quenched to become an amorphous particle [2]; in some cases the particle may even comprise a mixture of amorphous and crystalline components. It is very important to control the crystallinity of the particle as it affects the quality and stability of the final product. Crystalline particles, in general, offer stability during long term storage as the crystalline particles do not undergo phase transition changes[2, 3]. Amorphous particles may be relatively stable where a sufficiently low humidity is maintained during storage [4]. The crystalline state may also offer better dispersibility of particles[5-7].

In view of these past findings on how crystallinity or non-crystallinity contributes to the behaviour of pharmaceutical particles, there is a need to control the crystallization process of the droplet during rapid dehydration. The control of crystallization during droplet dehydration is further complicated by a wide range of crystallization behaviour of pharmaceutical materials. Some material crystallizes very rapidly during dehydration (e.g. amino acids, ionic salts, vitamin C, and mannitol)[1, 8, 9]. The time scale for crystallization nucleation and growth of these materials are in similar order to that of the particle formation time scale in spray drying[1]. Some materials are slow to crystallize e.g. lactose. These materials have a crystallization time scale order longer than the particle formation time scale [10]. This makes crystallization of this type of material difficult to achieve in
spray drying due to the rapid evaporation in spray drying which ‘quenches’ the droplet into amorphous particles [11-13]. For such materials, there are several approaches reported to increase the crystallinity of the formed particle, by processing parameter manipulation[13-18].

The effect of drying temperature has been investigated on crystallization and contrasting results were reported. Chiou et al [16] found the higher the drying temperature the higher degree of crystallization. This finding was subsequently confirmed with further experiment by Islam and Langrish [19] on high temperature spray drying. The similarity between these experiments was the utilisation of small benchtop spray drying [19]. Contrary to these results, Das et al [20] inferred that reduction in drying temperature intensifies the degree of crystallinity for lactose particles in a pilot scale spray dryer. It was found that rapid dehydration in a pilot scale spray dryer is more dominant phenomenon in reduction of crystallinity. Shakiba et al[21, 22] came to a similar conclusion and it was shown that the temperature should be designed for each material in relation to the kinetics of crystallization. On that basis the concept of “wet time” for particles was defined. The premise of the concept is that in-situ crystallization of particle depends on the time the particle is still wet; hence, the longer this time the higher propensity of crystallization. Wang et al [23] spray dried lactose mixed with casein as an additive and concluded this additive improved crystallinity because moisture evaporation was retarded; hence the moisture enhances the mobility of crystallization forming nuclei through the drying. Although the drying temperature is an important parameter in crystallization, this is only one aspect of a complicated process involving various parameters.

Apart from the drying temperature, the drying air humidity also has a major role although it has received little attention. Islam et al [13] investigated the effect of humidity
on the degree of crystallinity and deduced that high humidity increases the degree of crystallinity by keeping the particle glass transition at a lower degree. In similar veins, Shakiba et al [22] found that manipulation of humidity would be able to potentially alter the wet time of particle instead. However, in those past reports, the humidity of the entire drying chamber was elevated. Therefore, it was difficult to directly pinpoint how humidity mechanistically affects the in-situ crystallization process. Hence, this study aimed to investigate specifically the effect of humidity on the in-situ crystallization of particles by manipulating the local humidity at specific regions within the chamber to elucidate the mechanism in which humidity assists crystallization.

2.0 Materials and equipment

2.1 Material

Lactose is a typical powder carrier employed in inhaler and their surface characteristics play a critical role in drug delivery [24]. Lactose has relatively high glass transition temperature in comparison with other sugars[25]. For consistency, lactose solutions with 10% mass concentration were used for all the experiment except for the section investigating the effect of initial solute concentration on crystallization where 15% mass concentration was used. Solutions were prepared with distilled water in temperature between 15 to 25 °C and stirred for at least 4 hours to ensure mutarotation equilibrium is achieved[26].

2.2 Experimental equipment

A counter current spray drying tower developed in the Department of Chemical Engineering of Monash University was used. The tower height is 4m with a diameter of 0.6m
with a bottom opening (Fig. 1). Liquid feed was pressurized by compressed air and injected with a pressure atomizer from the top of the tower. Two different Am-fog nozzles were employed for generating different mean droplet sizes of 80µm and 120 µm; details of the nozzle droplet size distribution was given in a previous work[17]. Drying air was generated with the aid of 8 adjustable heat-guns which was mixed with compressed air for controllable flowrate and temperature. The drying air inlet was centred at the bottom where the hot drying air also entrains with the ambient flow coming from the bottom opening. The tower and the hot air generator were covered with glass wool to reduce heat loss through the walls. Temperature was measured at three different elevation points along the tower, (1) at drying air inlet, (2) at 1m from the bottom where air entrainment mostly developed and (3) at the top exit. The top outlet of the spray dryer is a flat plate containing 4 holes with diameter of 0.08m. Dry particles were collected from a tray installed at the bottom of the tower. The heating up time for tower to reach a stable condition was about 30 minutes.

This study required the increment of the local humidity at specific regions within the spray tower. To increase humidity, pure water was atomized into the spray dryer with the aid of a mist nozzle inserted into the tower. The nozzle was placed horizontally to humidify the cross section of the tower with spray angle of 25°. The maximum water injection was 4 L.h⁻¹; beyond this flow rate, the particles became sticky. In order to collect particles at different elevations of the tower, a sample collector was developed. This sample collector had a housing for a glass slide so that samples were collected directly on the glass slide which enabled direct imaging via optical microscopy without disturbing the particles.

2.3 Analytical tests
In this study XRD analysis was used to determine crystalline peaks delineating the main characteristics of crystallinity in the material. The XRD machine was Riguka miniflex capable of analysing six samples with maximum power feature of 40V and 15A. XRD analysis was carried out on the day of production to avoid phase change of particles during storage; hence, collected particles were stored in a desiccator before the XRD test. The analysis was done in the range of 0° to 40° as the main peaks of the lactose can be observed in this range with the scanning rate of 2°/sec. In addition, the XRD results were analysed by MAUD to filter the available noise in the raw data. In the analysis of the XRD result for lactose the main peaks of crystallinity were observed at 19°-19.6° and less intense peaks for alpha monomer lactose were at 12.4° and 16.2°[27].

DSC is conventionally used to characterize the change in thermal property (denoted by the change in heat flow across the material) during the phase change of material. This measurement was further used to characterize the degree of crystallinity. In this study a DSC machine (TA Q20) was utilized for a range of 40 to 180°C with a rate of 5°C/min heating. The DSC graph of pure alpha lactose showed two main endothermic peaks at around 145°C and 218°C which are respectively peaks of dehydration and melting of α-lactose monomer. In the samples containing amorphous lactose an exothermic peak was observed at around 173 °C which is related to the crystallization of amorphous content. The endothermic peak for lactose which appears at 144°C represents the loss of crystalline water or dehydration. The exothermic peak which is typical of amorphous lactose appears in the range of 160-170°C in which amorphous lactose recrystallize[28, 29]. The area under this exothermic peak denotes the required enthalpy for crystallization transition, the larger the area the lower the crystallinity. Sebhatu et al[30] calibrated the enthalpy of crystallization of lactose for DSC and compared it with XRD and micro-calorimetry. On this basis, the fully amorphous
lactose recrystallizes with 170 J/g energy liberation while this amount drops to 32 J/g for 16 % amorphicity.

In addition a free moisture content test was done for the whole generated samples. From each sample, 1 g of powder was kept in the oven in the temperature of 105°C for 5 hrs and the free moisture content was calculated from the change in mass.

3.0 Results and discussion

3.1 Spray drying with and without humidity elevation

The previous study of crystallization of sugars in the counter current spray dryer mostly focused on manipulating the drying temperature to achieve the best drying temperature for the sample materials[17]. It was found the higher degree of crystallinity was achieved at 110°C for lactose in a counter current dryer[17]. Therefore, this temperature was adopted for all experimental runs here. The inconsistency in the results of the previous work led us to monitor humidity more accurately. First, the experiments were run in different ambient humidity. Results in table 1 showed that with low ambient humidity (Run1), lactose particle did not crystallize and mainly amorphous particles were generated (according to XRD results Fig. 2). Run2 was carried out at higher ambient humidity and the XRD result (Fig. 2-b) indicated the existence of crystalline component in the particle. This is evidence that a higher humidity would assist to increase the crystallinity of particles, as reported for co-current spray dryers[13]. According to previous studies, increasing humidity gives rise to better crystallization of the particle[31].

Therefore, as a new strategy to control in-situ crystallization, a nozzle was installed at the air inlet pipe atomising pure water into the drying air before it enters the spray tower. In this manner the humidity within the whole tower was increased. This injection position is
shown as position A in Fig. 1. This method partially increased the crystallization of lactose particles, Fig. 2 (Run 3, table 1); although most of the particles were sticky due to contact with humid air throughout the entire trajectory within the tower. Therefore, increasing humidity of the whole dryer may have associated problem of insufficient dehydration of the particles. This might result in the need of exceedingly high inlet temperature to ensure sufficient drying.

To mitigate this effect, injection of pure water was carried out in the middle of the dryer, stage D Fig. 1, instead of bottom. As the humid air will flow upwards, the hot drying air regions below the elevation of injection will have low humidity to provide the driving force for more efficient dehydration. According to XRD result, Fig.2 for run 4, partially crystalline particles were achieved but this humidity elevation reduced drying temperature at the feed injection region at the top of the nozzle. Two important parameters for crystallization are nucleation rate and crystal growth, regardless of whether it is solid phase transition or liquid based crystallization precipitation. Both nucleation and crystal growth are partially affected by drying temperature and increasing the temperature improves both rates[32]. Hence, this temperature reduction may have an adverse effect on increasing the degree of crystallinity because it would also reduce the difference between particle temperature and glass transition temperature [19, 25]. The effect of this reduction of temperature due to water injection in the middle of the tower was alleviated by increasing the temperature of the pure water to the boiling temperature before injection. XRD results, Fig. 2, for this processing condition, run 5 table 1, showed that this strategy provided more efficient crystallization as delineated by two main distinct peaks of 12.4 and 16.5 not observed in the preceding runs. Although the scanning electron microscopy image does not provide information regarding the degree of crystallinity, it can be used as a qualitative
measure. Fig. 3 compares SEM images of different runs of table 1 in which shape of particles partially confirms the XRD results of Fig. 2. Specifically, existence of crystalline particles in Fig. 3, run 2 and run 5, is evident as there are particles with tomahawk structure in these images.

The results of the free moisture measurement, Table 1, shows that moisture content of above 3% was observed for all the runs. This represents the existence of amorphous lactose in all the runs because the free moisture content of crystal lactose is very low and it absorbs very low degree of moisture[33]. This is consistent with the results of the XRD analysis. However, amorphous samples are very susceptible to absorb ambient moisture content. This feature of amorphous particles would increase the error in measurement of free moisture content.

The results so far indicated that local humidity increase would be a more useful strategy to increase the degree of crystallinity. They generally were in agreement with previous studies in co-current spray dryer that humidity improves the crystallization process [13, 34]. Islam et al. [9] experimentally showed that the ambient humidity affects the in-situ crystallization process. Higher humidity increases the plasticization of the particles and hence decreases the glass transition temperature[25]. This gives rise to larger difference between the particle temperature and the particle glass transition temperature leading to higher rate of solid phase transition. Islam et al. [13] introduced high humidity at the inlet of the drying chamber, due to the co-current spray drying configuration, high humidity then pervades throughout the entire chamber. Therefore, it was difficult to precisely pinpoint on which duration of the drying history of the droplets/particles humidity significantly affects the in-situ crystallization process. A deeper understanding will be important to further elucidate the mechanism of the in-situ crystallization process. For better understanding of
the effect of local humidity manipulation, the next part of the experiment was carried out with local humidity manipulation at different elevations of the tower.

3.2. Spray Drying with manipulation of local humidity elevation

In a co-current spray dryer, injection of water vapour would increase the ambient humidity experienced by the droplets/particles throughout its trajectory subsequent to the moment of injecting water. In contrast, a counter current spray dryer has a different characteristic due to the reverse direction of the drying air. This permits local humidity injection in the tower without significant surge of humidity at subsequent trajectory of the particle. Therefore, there is a possibility for the droplet/particle to experience high humidity followed by low humidity drying conditions depending on the location of the water spray injection point; a feature not obtainable in the co-current spray dryer configuration. In the previous section, the water spray was introduced at 1.5m below the lactose feed atomiser, position D in Fig. 1. In the next series of experiments, the position of water spray was varied between 1-3 m below the feed atomiser (Fig.1). Initially, water spray at the position C (Run 1 table 2) resulted in slight increase in degree of crystallinity. XRD test (Fig. 4) showed the existence of crystalline component and the DSC test revealed the degree of crystallinity to be around 65%. Next, the water spray was moved down to stage D (Run 2 table 2) and similar results were obtained with a higher degree of crystallinity. The shorter peak of recrystallization in the DSC test, Fig. 5, confirmed the degree of crystallinity to be around 82%. In the next run, the nozzle was moved one level down, 2m from the top at position E (Run 3 table 2). It was very interesting that the highest degree of crystallinity was achieved at this elevation of water injection. The XRD results in Fig. 4 represented higher intensity peaks for this run and DSC test showed the lowest peak of recrystallization with the degree of crystallinity above 90%. When water was sprayed at the lower elevation, 2.5 m from the
atomiser in position E Fig. 1, lower degree of crystallinity was achieved (Run 4 table 2). According to DSC and XRD results, Figs. 4 and 5, the degree of crystallinity slightly reduced to 75% compared to the previous run. The position of water spray was further shifted down one more level to 3 m from the atomizer (Run 5 table 2). At this stage, the particles were slightly sticky and similar to that achieved when humidity was injected from the bottom of the tower. XRD and DSC tests Figs. 4 and 5, both confirmed a significant reduction of crystallinity at this stage. A series of free moisture content measurement was carried out for further interpretation of the DSC results (table 2). Although the free moisture content measurement roughly confirmed the DSC and XRD results, the comparison did not give rise to a definite outcome. This discrepancy can be observed in run 3 where the crystallinity was above 90% but with around 2% of free moisture. This may originate from the high moisture absorptivity of amorphous state affecting the results during collection. However, electron microscopy was carried out to thoroughly clarify the particle morphology (Fig. 6). These series of SEM images clearly illustrated the evolution of particle morphology under various stages of humidity raise. The available particles with tomahawk shape of crystal increased from the run 1 to run 3. So, almost all of the particles in Run 3 possessing this tomahawk structure. The availability of this crystal structure decreased in run 4 and run 5.

These results showed that higher degree of crystallinity could be achieved with water spray increasing the local humidity within the tower. There seemed to be an optimum position for water injection. We further investigated the significance of this optimum location for water injection and how it translates to the possible mechanism of crystallization in spray dryer.
3.3. Exploring the mechanistic significance of the optimal water injection elevation

Based on the literature, two possible explanations can be adopted to elucidate in-situ crystallization in spray drying. Firstly, the particle is formed by rapid drying into amorphous particle and humidity injection increases molecular mobility within the particle which contributes to facilitating molecular rearrangement and crystallization [14, 19]. In contrast, the other possible mechanism is that high humidity retards evaporation which increases the wet time of particle available for crystallization before complete solidification. Namely, the time in which particle is wet increases and time for nucleation and growth is available prior to solidification [25].

Hence, to shed more light on the effect of the drying history of particles on crystallization, particles were collected from different elevations of the dryer. The first test (Run 1, table 3) involved spray drying of the lactose at the inlet temperature of 110°C without humidity addition. It was interesting that sample collection from the top, stage B, to the middle of tower, stage D, showed the presence of liquid droplets (Fig. 8). However, some very fine particles were observed already formed but they flew out of the dryer from the top. The samples collected from one level down, stage E, showed partially formed particles. Fully solidified particles were only collected at stage F (2.5m from the top).

This experiment was repeated, run 2-table 3, while the feed temperature was increased to near the boiling temperature. Interestingly the height at which the fully formed particle was collected was shifted higher by approximately 0.5m, at stage E. Therefore, the partially dried particles were collected at stage D. This observation indicated how feed temperature would decrease the wet time of particle in the dryer. The next experiment (Run 3-table 3) was done with water spray at 1m from the top, stage C. The collected samples showed no significant difference from the experiment without humidity injection. Therefore, the drying
history of particles with humidity injection was fairly similar to the Fig.6. This observation would elucidate why humidity increase at this level did not affect degree of crystallization as observed previously, because it did not significantly change the drying and solidification history of the droplet. In the next experiment, run 4-table 3, humidity injection at 1.5 m from the top, stage D, resulted in slightly different drying history from the run without humidity rise. Collected particles at stage E were slightly sticky. In run 5-table 3, the humidity injection was moved one more level down, stage E. The collected samples from different elevations from stage B to stage E showed that particles were not formed. The particles were mostly formed at 2.5m (stage F) but they were still slightly sticky. Fully formed particles were collected at 3m (stage G).

During sample collection at stage G, many recirculated particles were collected at the back of the sample collector. This observation indicated an existence of a recirculation area at this height of the tower, where drying air jet entrained and mostly pushed up the particles dropping near the centre of dryer. Finally, humidity was injected from stage G, run6-table3. Expectedly, solid particles were formed slightly earlier than the previous run. Therefore, it can be observed that the local humidity injection at this stage had not increased the wet time of particle. Hence, particles were already formed before passing this local humid area. Results in table 3 can be visualized in Fig. 7.

The experiments showed that humidity injection is a useful strategy to increase crystallization prior to complete solidification. With the counter current spray drying configurations, local increase in humidity can also be manipulated by injecting water to vaporize at different elevations of the tower. Any local increase in air humidity will not pervade through the entire space of the chamber but only affect the local region of the water spray and the region above (‘downstream’ of the flow). This effectively isolates the
effect of high air humidity on the in-situ crystallization process to different segments or durations of the drying history of the droplet. Results showed that a relatively high degree of crystallinity was observed only when high humidity was introduced during the period of particle solidification transition, not when the droplet is still liquid-like or when the particle has solidified. This is a direct evidence to suggest that a significant in-situ crystallization process actually occurs during the intermediate stage of drying. A few reports in the literature allude to this finding. In the report by Das et al. [15, 20] on the crystallization of lactose in a pilot scale spray dryer, T-Tg of the particles at the outlet did not directly delineate the degree of crystallization observed in their experiments. This implies that the end point of the drying history of the particle may not be a main factor controlling the in-situ crystallization process. Woo et al. [35] in their analysis of relatively larger single droplet drying also noted that there is a “critical crystallization period” at the intermediate stage of drying, the duration after the wet bulb period when the droplet temperature starts to rise, in which significantly higher degree of crystallinity is generated, relative to the crystallinity generated once the solidification is completed [35, 36]. The current results suggest that the mentioned critical condition concept is also applicable to a relatively short period of drying time for the particles in an actual spray dryer; where the moisture content of droplet is rapidly reduced.

What does this mean in terms of the mechanism of the in-situ crystallization process? This suggests that solid phase transition, the development of crystallinity from solidified particles (albeit with low level of moisture content) may not be the sole mechanism controlling the in-situ crystallization process for slow-to-crystallize materials such as lactose. Analysis on the moisture content and the calculated glass transition temperature of the particles collected also supported this notion (Table 2). The calculated glass transition
temperature of particles were within the range of 72–95°C based on the moisture content of particles in Table 2. This glass transition temperatures were calculated based on the approach of Hancock and Zografi [25]. While the top outlet temperature of the counter current tower is around 85-90°C, the central annulus inlet air used in the experiments were 180-200°C and the region about 0.5 m above the central annulus hot air inlet had an average measured temperature of approximately 105-110°C. This latter temperature is more representative of the overall temperature in the chamber as the central annulus air will mix with the cooler air aspirated into the chamber. Nevertheless, as the particles travel downwards in a counter current manner towards the hotter bottom inlet region, it would have experienced progressively higher temperature (above its glass transition temperature) giving it higher plasticizing potential for solid phase crystallization transition. However, high degree of crystallinity was only observed when the intermediate stage of drying was manipulated with humidity elevation.

To further support this analysis, more runs were undertaken to give longer wet time by changing the droplet size. It was speculated that a longer wet time can be achieved by larger droplet size; possibly reducing the need for humidity injection. Hence, two experiments were carried out with a different nozzle generating larger droplet size. The drying temperature was adjusted to 110°C and the feed concentration of 10%. In the first test, run1—Table 4, feed in the ambient temperature was atomized. DSC and XRD analysis of this test showed very low degree of crystallinity (Fig. 9 and Fig. 10). In the next experiment, run2 Table 4, the feed temperature was elevated to investigate effect of quicker supersaturation for a larger droplet. Both of XRD and DSC results confirmed a slightly higher degree of crystallinity relative to the control run; nevertheless, the degree of crystallinity was still significantly lower than the runs with humidity injection. All these results so far indicated
that the manipulation of only the intermediate stage of drying, may provide the most significant effect in the control of in-situ crystallization in spray drying.

3.4 Investigation into in-situ liquid phase crystallization process

In the prior sections, it was discovered that the glass transition temperature theory may not be the only mechanism to elucidate the in-situ crystallization of particles in spray dryer. The other possible mechanism for spray drying in-situ crystallization for slow-to-crystallize material, which is not commonly discussed, is the liquid phase nucleation and growth mechanism. Based on the classical theory of crystallization, nucleation occurs only after the droplet becomes supersaturated, from which the growth of the nuclei then proceeds to form crystals. Therefore, the next set of experiments were undertaken to assess if it is possible to manipulate these two processes for slow-to-crystallize materials by (1) changing the initial concentration of the feed material and (2) elevating the feed temperature.

3.4.1 Effect of initial solution concentration on in-situ crystallization

Drawing inspiration from reports on the co-current spray drying of fast to crystallize materials (leucine) [37], one strategy to enhance such nucleation and growth process is to manipulate the drying history of the droplet so that supersaturation is rapidly achieved. This will then allow a longer time for the droplet to undergo the nucleation and growth process while still within the drying chamber. High 15% concentration lactose feed was then spray dried without humidity elevation in the tower with the aim of achieving supersaturation in a more rapid manner. It is noteworthy that the supersaturation of
lactose at 25°C is about 22 gr/l. Unexpectedly, the particles were relatively lower in crystallinity when compared to the 10% concentration lactose feed runs (Run 1 – Table 5). Particles were collected at different stages of the tower and it showed particle formation occurred nearly one stage earlier than the 10% concentration runs. Namely fully formed particle was observed at stage E, 2m from the feed atomizer whereas for the 10%wt runs, solid particles were observed only at about 2.5-3m from the top.

Water was then sprayed into the tower at different stages to observe its effect on crystallization for the higher feed concentration. Humidity was firstly injected at stage E, 2m from the feed atomizer (Run2 table 5). Particles collected at different stages of tower showed humidity injection at this stage did not result in increasing wet time of particles and the collected samples were thoroughly similar to the one without humidity injection. Humidity injection was then carried out at one stage higher, 1.5m from top stage D, and (Run 3 table 5). The SEM results revealed existence of crystalline lactose and XRD (Fig.12) confirmed slight improvement in the degree of crystallinity in comparison with the previous run. However, compared to the 10% concentration runs, the degree of crystallinity was still relatively lower. The observation of the particles collected at stage D indicated slightly sticky particle compared to the previous run. Fully formed particle was collected at 2-2.5m below the atomizer. This means that humidity injection partially postponed the drying of particles and increased the wet time of particle. In the next run, humidity injection was done at 1m from the top, but according to the XRD results, Fig. 12, this did not effectively influence the degree of crystallinity. Particle collection at stage D, 1.5 m from atomizer, showed almost formed particles at this stage and fully dried at stage E.

This set of experiments showed that for the spray drying of such slow to crystallize materials, using a counter current spray drying approach, a more rapid attainment of
supersaturation may not necessarily provide a longer time for the nucleation and growth process during drying. This is in contrast to past report on fast to crystallize materials utilizing this strategy. Nevertheless, if higher initial feed concentration is inevitable, the manipulation of local humidity will still offer an avenue to control the in-situ crystallization process.

3.4.2 Effect of feed preheating temperature on in-situ crystallization

From the classical theory of crystallization, the nucleation and growth process are also affected by the temperature of the crystallizing system [32, 38]. A higher temperature would amplify the creation of nuclei and the growth process [32]. Therefore, the effect of preheating the lactose feed material to elevate temperatures on the in-situ crystallization process was investigated. While the droplets may cool in the initial constant period of drying, it was hypothesized that the elevated temperature may elevate the overall temperature history of the droplet during drying.

Hence, in this set of experiments, feed temperature was elevated to around 110°C under pressure before injection. The first test (Run 1 table 6) was carried out without humidity injection. Similar to previous tests, particles were collected at different heights within the chamber. These collected particles showed very early particle formation; formation of particle was completed at stage C, 1m after atomization. Also, XRD results, Fig. 13, displayed no peak of crystallinity and the yield was totally amorphous. It was observed, however, that the level of free moisture content for this particles which was as low as 3% and the particles were very free flowing even after two months storage. For the rest of the tests, injection of humidity was carried out at the different elevations of the tower from
stage C and D respectively to observe its effect on crystallization. Similar to the previous run almost no noticeable crystallinity was observed in the XRD results of this series, Fig. 13. In light of these observations, the feed temperature was then reduced to 80°C (Run 5 table 6) to decrease very early particle formation that was observed in prior tests. Particles collection from various heights showed that they are formed around 1.5-2 m below the atomizer. Humidity elevation carried out at 1m from the top, stage C (Run 6 table 6), showed there is negligible effect on the degree of crystallization compared to the Runs without feed temperature elevation (Fig. 13). The moisture content of that run was also above 3.5%. In the next experiment (Run7, table 6) humidity injection was done at 1.5m from the top. The collected samples at various elevations revealed dried particle at 1.5-2 m after atomizer. The XRD result showed improvement in the degree of crystallization but the moisture content was around 3.4%. The collected particle of different heights of the tower also indicated a delay in particle formation. Hence, particles were formed at 1.5m but fully dried particles were achieved at 2m.

This series of experiments revealed that increasing the feed temperature does not promote in-situ crystallization in spray drying of slow to crystallize materials. So, even in the case of water spray in the tower combined with feed temperature elevation (Runs 6 and 7), the degree of crystallinity is less than the Runs without elevation of feed temperature. Similar to the elevation of feed concentration, the elevation of feed temperature enhances drying and effectively reduces the mobility inside the particle to allow for growth of nuclei, leading to the formation of amorphous particles instead. Both of these results further suggest that a less rapid initial particle formation process will provide a higher propensity for in-situ crystallization in spray dryers.
4.0 Conclusions

Producing engineered particles with controlled crystallinity via spray drying is important for the pharmaceutical and food industries. Recent work confirmed the feasibility of in-situ crystallization control with spray dryer. This study showed the importance of the critical period for in-situ crystallization corresponding to the intermediate stage of drying. Extending the critical period of crystallization was achieved with local humidity manipulation, which effectively increased the wet time of the droplet in supersaturation condition. In this vein, the supersaturation nucleation and growth mechanism may be a suitable mechanism to control the in-situ crystallisation process in spray drying. Various strategies were evaluated, by varying the feed concentration, feed temperature, injection mist in different heights and varying droplet size, to control this mechanism. Analysis revealed that increasing the droplet size could be one important control parameter to increase the degree of crystallinity in the particles; although the degree of crystallinity developed is lower than that produced by local humidity manipulation. Results from this work will be useful as a basis for future work on the control of in-situ crystallization in spray dryers for slow to crystallize materials.

5.0 References


Figure 1. (left) schematic of the spray drying tower; (right) position of humidity injection and sample collection at different heights of spray dryer.
Figure 2. XRD spectrum of lactose in the same processing condition but various humidity related to the runs 1-5 in table 1.
Figure 3. SEM result for spray drying in different humidity conditions with regard to table 1
Figure 4. XRD spectrum for spray drying with humidity injection at different stages a) stage E, b) stage D, c) stage F, d) stage C, e) stage G
Figure 5. DSC results for spray drying of 10% (w/w) lactose with humidity injection in different height of the tower.
Figure 6. SEM image related to the lactose spray drying with humidity injection with regards to table 2 processing condition.
Figure 7. Visualization of collected samples in different heights of the spray dryer based on table 3; hollow sphere represents droplet, pattern sphere represents formed particle, solid sphere represents dried particle.
Figure 8. Optical microscopy of collected samples across different height of dryer for drying in 110°C without humidity injection: referred to different stages of spray dryer in Fig.3
Figure 9. XRD spectrum for particle spray dried with initial droplet size of 120µm
Figure 10. DSC results for different processing conditions
Figure 11. samples collected from different height of spray dryer, First row) lactose 15% without humidity elevation, second row) lactose 15% with humidity elevation.
Figure 12. XRD spectrum for spray dried lactose particles of 15% w/w with a) humidity elevation at stage D, b) humidity elevation at stage C, c) humidity elevation at stage E, d) without humidity elevation.
Figure 13. XRD spectrum for spray dried lactose with elevated temperature a) to g) are related to the run 1 to 7 in table 6.
Table 1. Spray dried lactose 10%(w/w) in various processing conditions

<table>
<thead>
<tr>
<th>Run</th>
<th>Humidity</th>
<th>Injection</th>
<th>Absolute humidity Inlet/outlet (gr/kg)</th>
<th>Average inlet/outlet temperature range (°C)</th>
<th>Velocity (m/s)</th>
<th>Results (crystallinity, moisture content)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td></td>
<td>8/14</td>
<td>105/92</td>
<td>0.31</td>
<td>No crystalline, 3.8%</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td></td>
<td>21/28</td>
<td>110/95</td>
<td>0.31</td>
<td>Existence of crystalline, 3.5%</td>
</tr>
<tr>
<td>3</td>
<td>stage A</td>
<td>25°C</td>
<td>9/25</td>
<td>105/78</td>
<td>0.31</td>
<td>Sticky, 5%</td>
</tr>
<tr>
<td>4</td>
<td>stage D</td>
<td>25°C</td>
<td>9/26</td>
<td>105/77</td>
<td>0.31</td>
<td>No crystalline, 4%</td>
</tr>
<tr>
<td>5</td>
<td>stage D</td>
<td>100°C</td>
<td>9/30</td>
<td>110/96</td>
<td>0.31</td>
<td>Existence of crystalline, 3.3%</td>
</tr>
<tr>
<td>Run</td>
<td>Absolute humidity gr/kg</td>
<td>Average inlet/outlet temperature range °C</td>
<td>Humidity injection height(m)</td>
<td>Free moisture content (%)</td>
<td>Enthalpy of crystallization (J/g) and degree of crystallinity</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td>------------------------------</td>
<td>--------------------------</td>
<td>------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10/31</td>
<td>110/98</td>
<td>1(C)</td>
<td>3.2</td>
<td>57, 65%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11/32</td>
<td>110/97</td>
<td>1.5(D)</td>
<td>2.2</td>
<td>34, 82%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10/31</td>
<td>110/97</td>
<td>2(E)</td>
<td>1.7</td>
<td>16, above 90%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10/31</td>
<td>110/96</td>
<td>2.5(F)</td>
<td>2.7</td>
<td>48, 75%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>9/30</td>
<td>110/97</td>
<td>3(G)</td>
<td>4.5</td>
<td>78, 50%</td>
<td></td>
</tr>
<tr>
<td>Run</td>
<td>Feed temperature</td>
<td>Absolute inlet/outlet humidity gr/kg</td>
<td>Average inlet/outlet temperature range °C</td>
<td>Humidity injection height(m)</td>
<td>Height of formed particle</td>
<td>Height of fully dried particle</td>
</tr>
<tr>
<td>-----</td>
<td>------------------</td>
<td>-------------------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>10/17</td>
<td>110/98</td>
<td>No</td>
<td>2</td>
<td>2-2.5</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>11/18</td>
<td>110/101</td>
<td>No</td>
<td>1.5</td>
<td>1.5-2</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>10/31</td>
<td>110/96</td>
<td>1(C)</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>10/31</td>
<td>110/97</td>
<td>1.5(D)</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>11/32</td>
<td>110/96</td>
<td>2 (E)</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>11/32</td>
<td>110/96</td>
<td>2.5(F)</td>
<td>2</td>
<td>2-2.5</td>
</tr>
</tbody>
</table>
Table 4. Spray dried lactose 10% (w/w) humidity injection at different levels

<table>
<thead>
<tr>
<th>Run</th>
<th>Average Droplet size(µm)</th>
<th>Absolute inlet/outlet humidity gr/kg</th>
<th>Average inlet/outlet temperature range °C</th>
<th>Feed temperature °C</th>
<th>Free moisture content (%)</th>
<th>Enthalpy of crystallization(J/g) and degree of crystallinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>10/23</td>
<td>110/90</td>
<td>22</td>
<td>4.5</td>
<td>96, 35%</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>11/24</td>
<td>110/92</td>
<td>85</td>
<td>3.7</td>
<td>57, 65%</td>
</tr>
</tbody>
</table>
Table 5. Spray dried lactose 15% (w/w) in various processing conditions

<table>
<thead>
<tr>
<th>Run</th>
<th>Average Droplet size(µm)</th>
<th>Absolute inlet/outlet humidity gr/kg</th>
<th>Average inlet/outlet temperature range °C</th>
<th>Humidity injection height(m)</th>
<th>Height of fully dried particle</th>
<th>Results, enthalpy of crystallization, moisture content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>8/15</td>
<td>110/98</td>
<td>Non</td>
<td>2</td>
<td>Amorphous, 3.1%</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>8/29</td>
<td>110/97</td>
<td>2</td>
<td>2</td>
<td>Very low degree of crystallinity, 3.5% agglomerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crystalline, 67(J/gr), 3%</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>9/30</td>
<td>110/97</td>
<td>1.5</td>
<td>2-2.5</td>
<td>Low degree of crystallinity, 94(J/gr), 3.5%</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>9/30</td>
<td>110/97</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Run</td>
<td>Absolute humidity gr/kg</td>
<td>Average inlet/outlet temperature range °C</td>
<td>Humidity injection height(m)</td>
<td>Feed Temperature °C</td>
<td>Height of fully dried particle (m)</td>
<td>Results, enthalpy of crystallization, moisture content</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
<td>---------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>110/103</td>
<td>Non</td>
<td>110@6bar</td>
<td>1-1.5</td>
<td>Amorphous, high yield, 3%</td>
</tr>
<tr>
<td>2</td>
<td>9/30</td>
<td>110/104</td>
<td>1</td>
<td>110@6bar</td>
<td>1-1.5</td>
<td>Amorphous, low yield, 3.3%</td>
</tr>
<tr>
<td>3</td>
<td>9/30</td>
<td>110/104</td>
<td>1.5</td>
<td>110@6bar</td>
<td>1-1.5</td>
<td>Amorphous, low yield 3.4%</td>
</tr>
<tr>
<td>4</td>
<td>9/31</td>
<td>110/103</td>
<td>0.5</td>
<td>110@6bar</td>
<td>1-1.5</td>
<td>Amorphous, highly agglomerated, high yield, 3.2</td>
</tr>
<tr>
<td>5</td>
<td>9/30</td>
<td>110/98</td>
<td>No</td>
<td>80</td>
<td>1.5-2</td>
<td>Amorphous, 4%</td>
</tr>
<tr>
<td>6</td>
<td>9/30</td>
<td>110/98</td>
<td>1</td>
<td>80</td>
<td>1.5-2</td>
<td>Existence of crystalline 101 (J/gr), 3.7%</td>
</tr>
<tr>
<td>7</td>
<td>9/31</td>
<td>110/97</td>
<td>1.5</td>
<td>80</td>
<td>2</td>
<td>Existence of crystalline, 81(J/gr), 3.2%</td>
</tr>
</tbody>
</table>
Graphical abstract

Increasing rate of crystallization with local humidity manipulation in spray dryer
Research highlights

- Investigation of effect of humidity on in-situ crystallization in counter current S/D
- Study on the effect of local humidity elevation for achieving highest degree of crystallization
- Discovery of mechanism of in-situ crystallization via particle collection from different heights
- Comparing impact of various effective parameters of crystallization on degree of crystallinity