In-situ Crystallization via Counter-Current Spray-Dryer: Mechanism of Particle Crystallization through spray drying

Soroush Shakiba

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Department of Chemical Engineering

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Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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Abstract

Production of crystalline particle having engineered crystallinity is important as it affects the efficiency and delivery of drug delivery. Spray drying is a conventional and ubiquitous particle manufacturing process. The use of spray drying in the production of crystalline particles, however, is not widely investigated. In this thesis, counter current spray drying (CCSD) was used for the production of two widely encountered pharmaceutical excipients, lactose and mannitol. The first part of this thesis showed that in contrast to the typical co-current spray drying reported in this area, the CCSD provided higher residence time and suitable drying history for the control of in-situ crystallization within the drying chamber. Crystalline lactose were produced by strategic elevation of drying temperature while mannitol crystalline particles generation required the elevation of the feed temperature; reflecting the different control strategies required specific to the different crystallization behaviour of the material. Different CCSD in-situ crystallization strategies were further explored in this part of the thesis. The second part of the thesis investigated in greater detail the mechanism in which in-situ crystallinity occurs within the spray drying chamber. The experiment results supported the idea of an ‘effective wet time’ which can be used for particle crystallinity control. This was unveiled by carefully manipulation of local humidity, by additional pure water atomization, within the CCSD tower. It was found that there is a critical crystallization period in the intermediate period of the droplet drying history, in which if extended, can be used to increase the crystallinity of spray dried particles. This finding is in contrast to existing understanding of in-situ crystallization control in which the latter part of the drying history was thought to be the dominant phase of the drying history responsible to in-situ crystallization control. In the third part of this thesis, a new predictive model was developed as a predictive tool for in-situ crystallization. The premise of the model utilizes the operating conditions of the spray drying to calculate the indicative time duration available for crystallization. This is then coupled with the crystallization behavior of the spray dried material. The development of the model led to a modified dimensionless Damkohler (Da) number which compares the timescale available for crystallization and the crystallization timescale of the material. This model was experimentally validated with the spray drying of mannitol. The model was capable of indicating conditions leading to different size of crystalline mannitol formed during the spray drying process.

Publications from the thesis

Original Research Paper:

In-situ crystallization of particles in a counter-current spray dryer
S Shakiba, S Mansouri, C Selomulya, MW Woo
Advanced Powder Technology 27 (6), 2299-2307

The role of the intermediate stage of drying on particle in-situ crystallization in spray dryers
S Shakiba, S Mansouri, C Selomulya, MW Woo
Powder Technology 323, 357-366

Dimensional analysis of in-situ crystal formation in droplet undergoing rapid dehydration
S. Shakiba, S. Mansouria, C. Selomulyaa, M.W. Woo
Submitted to: International national Journal of Pharmaceutics (under review)

Review Paper:

Controlling in situ crystallization of pharmaceutical particles within the spray dryer
MW Woo, MG Lee, **S Shakiba**, S Mansouri
Expert opinion on drug delivery 14 (11), 1315-1324
(contribution: 40% of the paper)

‘Thesis Including Published Works’ Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes two original papers published in peer reviewed journals and 1 original unpublished publication. The core theme of the thesis is about in-situ crystallization during spray drying process and understanding the mechanism of particle formation. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself working within the Department of Chemical Engineering under the supervision of Dr Meng Wai Woo, Dr. Shahnaz Mansouri and Professor Cordelia Selomulya.

(The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research

In all chapters, I have been the first and main author and my contribution to the work involved designing the setup and experiment, laboratory work, developing models and calculations, writing up research papers in association with my supervisory team Dr. Meng Wai Woo, Dr. Shahnaz Mansouri and Prof Cordelia Selomulya.

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: ***(Soroush Shakiba)*** [redacted] **Date:** 09/02/2019

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student’s and co-authors’ contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main supervisor signature: [redacted] Date: 25 July 2018

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Chapter One

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1 Introduction

Production of crystalline powders makes up a significant portion of the processing of pharmaceutical, food and chemical materials. A variety of methods could be utilized for the manufacturing of crystalline particles. This necessitates the selection of suitable manufacturing process based on the specification of the product, cost and the pace of manufacturing. One of the methods that has recently come to center of attention for manufacturing engineered particles is spray drying. Spray drying is a well-established method in which dissolved material (in the aqueous or other solvent medium) is atomized into a big chamber to contact with hot air gas. During this process, the solvent is evaporated and the remaining solute is formed into the particulate powder. Due to flexibility of this method for controlling various processing parameters, this process is capable to be used for generating engineered particles.

Although this method has advantages in processing engineered particles, this process is hitherto mainly used for processing amorphous particles. At the core of spray drying is a very rapid droplet evaporation and solidification process while time is one of vital factor in crystallization. The nature of this process hinders the manufacturing of crystalline particles, mainly because such rapid solidification time scale does not facilitate structure rearrangement (crystallization) of the solutes.

Nevertheless, spray drying has capability to produce high volume of powder within a continuous and economical process. Therefore, there is strong motivation to further research to advance this powder processing technique for the manufacturing of crystalline powder. Hence, this study aims to discover the feasibility of utilizing spray dryer for manufacturing crystalline pharmaceutical and food particles. On this basis, the following research gaps were found in the literature and considered as the objective of this thesis.

There are limited studies reported in the literature on the in-situ crystallization process within the spray dryer. All the studies reported so far were devoted to co-current type of spray drying configuration in which the atomized droplets come immediately into contact with hot drying air, experiencing very rapid evaporation at the beginning of the droplets' drying history. In the counter current configuration, the droplet would initially experience cooler dehydrating air and may potentially experience less rapid initial evaporation. The first objective of this thesis was to investigate if such contrastingly different drying history of the counter current spray drying process can be utilize to control and induce in-situ crystallization within the spray drying chamber.

Amongst the reported work in this area, earlier reports showed that the in-situ crystallization process can be controlled and it largely governed by the outlet conditions of the spray dryer. This delineates to the solid phase transition being the primary mechanism by which in-situ crystallization can occur. Therefore, materials with different crystallization behavior, sucrose, lactose and mannitol, were experimentally investigated, Recent reports showed that the outlet controlled solid phase transition mechanism may not be applicable in larger scale spray dryers. This showed that the basic mechanistic understanding of in-situ crystallization was far from complete. Therefore, the second objective of this thesis was aimed at understanding the basic mechanism by which in-situ crystallization will occur within the time scale of spray drying.

The third objective of this thesis aimed at developing a predictive framework to predict in-situ crystallization in spray drying. Currently, predictive models available attempts to provide indirect indication of the in-situ crystallization by computing the evaporation characteristics, glass transition characteristics, and the crust formation characteristics of the sprayed droplets. There is yet to be a model which effectively and directly captures the crystallization characteristics of the spray dried material. On this basis, the aim was to link well-established crystallization theory and tailor them to the modelling of the rapid evaporation of droplets.

In the following chapters, the research gaps will be discussed in detail and the finding and methods will be illustrated to address these three objectives of the thesis.

Chapter two

2 Literature Review

2.1 Introduction

Spray drying is widely used in the pharmaceutical industry to produce dry powder, excipient and active pharmaceutical ingredients. One advantage of spray drying is that the pharmaceuticals are dehydrated and formed in a particulate form in a one step process without the need for additional milling; providing a way to control the particle size distribution of the product and to minimize product modification during the milling process. The premise of the spray drying process lies in spraying the pharmaceutical materials into droplets, into a hot air environment, which dehydrates the droplet into micron or submicron size solid particles [1][2]. In view of the rapid evaporation of the micron size sprayed droplets, it is very common for particles to be produced in the amorphous state, due to the minimal solidification time available for ordered crystalline molecular rearrangement. Formation of crystalline particles, however, occur to different degrees depending on the characteristics of the material. Lactose, for example, is typically spray dried to produce amorphous product [3]. In contrast, mannitol and glycine are often spray dried into very highly crystalline forms [4][5]. Crystallinity formed during spray drying may appear as an agglomeration of highly distinct minute crystals forming the particle or may be a combination of crystalline region infused with amorphous regions forming the particle (for pure material). In-situ crystallization may also be encountered in the spray drying of solid dispersions [6][7]. Although the spray drying crystallization process of these pharmaceuticals are highly material dependent, the literature shows that they can be manipulated or controlled to certain extent. There are many incentives for controlling the crystallization process during spray drying which will be described in the following sections.

2.2 Why control in-situ crystallization in spray dryers?

The characteristics of crystals formed during spray drying determine the surface energy of the particles [8][9]. This is an important functionality, which has to be effectively controlled in the spray drying of pharmaceuticals for pulmonary delivery. Because surface energy of particles significantly affect flowability of the particles. In spray drying of mannitol, the size of the crystal formed was found to affect the rugosity, surface roughness, of the particles. This determines how a micronized drug adhering onto the crystals; between the minute crystals on the surface or on the minute surface crystals. This settling is in addition to the accumulating of drugs at the deformed cavity of the particles, formed due to shrinkage of the spray dried particles [10]. There are reports on how such characteristics can be controlled and characterized [13][14]. Therefore, the morphology (including shape, size and surface structure) of the excipient, as a drug carrier, plays an important role in effectiveness of the medicine [11, 12]. For inhaler applications, excipients are used as a carrier for API particles and the morphology of the excipient particles significantly influence efficacy of the medication. Excipients with low degree of crystallinity are very prone to phase change and spoiling active pharmaceuticals. Having large surace area let the excipients to carry more micronized drugs. High surface energy of excipient would results in poor dispersion of drugs and also affecting flowability of excipient [14, 15].

One of the important reason for having spray dried particles with a higher degree of crystallization is that they are more shelf-stable [16][17]. This is because the dehydrated material in the crystalline form is less susceptible to phase changes leading to caking and product degradation typically observed in amorphous materials. Such phase transitions may be even more prevalent if the product is stored or transported in conditions of relatively high humidity and high temperature. However, in contrast, the advantage of having amorphous particles is that it improves the dissolution rate of the particles [18]. In the case of medical tablets, the dissolution rate of excipient determines the required time for medicine to be absorbed though stability will remain a challenge and requires extra strategies to keep particles stable [13]. To that end, some other micronization technique such as milling may also be useful, as the mechanical breakage of the particles will generate high surface amorphicity [19].

Having particles with an amorphous matrix is also useful in the preservation of bioactive in spray dried powders. This is widely encountered particularly in the spray drying of proteins with excipients in the product formulation. In view of the incompatibility of proteins with non-crystallization reducing sugars such as lactose, there have been many reports on the spray drying of proteins with excipients such as mannitol [17][20][21]. The main complexity is on strategies to prevent crystallization in the protein-excipient powders. Hulse *et al.* [20] evaluated the crystallization behaviour by incorporating lysozymes and trypsin into the protein-mannitol formulation; with trypsin exhibited higher crystallization inhibition effect when compared to lysozyme. Constantino *et al.* [17] evaluated the stability of mannitol when combined with rhuMAbE25 antibody. It was found that the there is a threshold of 40%wt mannitol loading before spray dried particles crystallize resulting in lower protein stability. Ajmera and Scherlieb [22] also cite a combination of amino acids to prevent crystallization in the particle matrix for protein preservation during spray drying. It is noteworthy that a solid pharmaceutical could possess both of crystalline and amorphous states to some extents [1]. These reports cited pertain mainly to formulation control for crystallization inhibition. Other strategies will be further discussed in greater detail in this review. In view of the importance of crystallinity or non-crystallinity in spray dried particles, this review will present some useful strategies to control the in-situ crystallization process in spray drying.

2.3 Current spray drying in-situ crystallization strategies

The term *in-situ crystallization* deserves some clarifications as the focus of this review is only on controlling the crystallization process occurring *within* the spray drying chamber. Most reports on spray drying of pharmaceuticals often involve analysis of the stability of particles of the spray-dried products (preventing crystallization) or in using subsequent storage treatment under different humidity or temperature degrees to modify the crystallinity of the particles [20]. These crystallization processes differ from that of in-situ crystallization in spray dryers, mainly in terms of the time scale available for crystallization. Secondly, the crystallization process within the spray-drying chamber is occurring simultaneously with the droplet dehydration process. This is a physical feature not present in storage crystallization or other crystallization process encountered in the pharmaceutical industry such as the hot melt, the antisolvent precipitation or the pan crystallization technique [23-26].

An important feature in spray drying is that evaporation is typically very rapid and most of the moisture is removed from the droplet in the region near the atomizer; particles are formed near the atomizer region, albeit with traces of free and bound moisture. In other words, even if large spray dryers are used, the particle formation time is relatively short in the order of fraction of a second or a few seconds. Furthermore, most reports on the mechanistic aspect of in-situ crystallization in spray dryers were produced using small laboratory scale spray dryers, eg. the Buchi spray dryer, leading to even shorter evaporation time scale. Regardless of the size of the spray dryer the key strategy is to manipulate the evaporation time, albeit relatively short, to control the nucleation and growth of crystals (or for some materials, to control solid phase transition) within the dehydrating droplet. The following sections are a few strategies currently reported for such in-situ crystallization control.

2.3.1 Using the chamber outlet temperature as a control parameter

For the spray drying of fast to crystallize material, extensive work has been done on mannitol and amino acids. There are reports in which the outlet temperature was used as an indication of the drying rate within the chamber. Maas *et al.* [27] found that, from a small-scale dryer, higher outlet temperature which was claimed to delineate higher evaporation rates, produced larger crystals. Two mechanisms for mannitol in-situ crystallization were proposed to elucidate this trend. For the lower outlet temperature, the conventional saturation precipitation by nucleation and growth was suggested. For the higher outlet temperature, it was proposed that the rapid evaporation initially forms a metastable viscous droplet with very high supersaturation from which nucleation is then followed by rapid growth of the crystals, leading to large crystals. These two mechanisms were supported by observation of dehydrating mannitol droplets on a heated microscope stage.

Littringer *et al.* [28] further observed similar trend in their experiments on a slightly larger scale spray dryer, the Niro mobile minor. Similar mechanism as suggested by Maas *et al.* [27] was adopted in explaining their experimental trend. Interestingly, when the outlet temperature was increased to above

150 °C, non-spherical mannitol particle were produced. It was assumed and deduced that molten mannitol was produced which solidifies and crystallizes within the drying chamber [27]. Within the same report [27], contrasting trend was observed in the larger long pilot scale dryer where higher inlet temperature produced smaller crystals. The authors proposed several possible mechanisms leading to the contrasting trend and one of the factors identified was that larger droplets were sprayed in the long pilot scale dryer, which resulted in a longer evaporation time. However, no exact and definite mechanism leading to the discrepancy was identified.

This opposing trend in using the outlet temperature to control the in-situ crystallization of mannitol was further observed in the experiments of Littringer *et al.* [10] with the large-scale spray dryer. A more complex behavior in which an intermediate outlet temperature produced the smoothest (finest crystals, nano size) particle surface when compared to the larger crystals produced at the high and low extremes of the outlet temperature, 80 and 130˚C. In a later work on the large-scale spray dryer [10][4], more physical interpretation was given to the effect of the outlet temperature. Littringer *et al.* [10] noted that the inlet air temperature and the liquid feed rate had the highest influence on the crystallinity of mannitol particles. Higher temperature gave smoother surface and vice versa. In contrast, higher feed rate gave rougher particle surface while lower feed flow rates produced smoother particles. It is noteworthy to mention this feed rate can only be defined base on capacity of the dryer and also affect the outlet temperature as it controls the amount of evaporation within the drying chamber. Therefore, contrasting results from these past reports are evidences that it may be insufficient to use the outlet temperature as a sole control parameter to directly delineate the drying rate. The usage of the conventional outlet temperature as a control parameter of the drying rate to manipulate the in-situ crystallization process may be a dryer scale dependent making it a less reliable control parameter.

For slow to crystallize material, such as lactose as opposed to mannitol, it was found that higher inlet temperature resulted in higher degree of crystallinity [29]. This was attributed to the higher plasticization at the elevated temperature resulting in solid phase transition of the amorphous lactose formed in the initial instance of the rapid drying process. In a similar vein, further examined by Islam *et al.* [30], the same effect can be obtained by increasing the humidity within the spray dryer; this is attributed to the glass transition temperature depression due to plasticization of the particles at higher moisture. These findings were observed from the small scale Buchi spray dryer.

Similar contrast in trend was observed for the larger pilot scale spray dryer. With longer residence time within the chamber, the opposite was then observed in which lower temperature resulted in the highest degree of crystallinity [31]. This was supported by further work indicating the excessive initial dehydration may lead to sticky particles and not production of particles with high degree of crystallinity [32]. It was suggested in the report that lower temperature may allow a ‘wetter’ particle drying history allowing more in-situ crystallization. Further analysis in the latter work also revealed that analysis of the T-Tg at the outlet were negative (Tg higher than T), even for the runs with high degree of crystallinity. This may suggests that the usage of the outlet conditions may not be suitable to characterise the crystallization potential of a large scale spray drying operation.

In view of these evidences, there is a need to find a more representative approach, other than the outlet temperature conventionally used to characterize the in-situ crystallization potential of a spray drying operation.

2.3.2 Exploring the intermediate stage of drying as a control parameter

Maa *et al.* [33] initially and briefly provided a few suggestions to characterize the drying behaviour of the spray dryer: (1) to use the arithmetic or logarithmic mean temperature difference between the inlet and outlet temperature of the spray dryer or (2) to use the difference between the wet bulb temperature measured and the outlet temperature. However, from the small Buchi lab scale spray dryer used in their experiments, the internal temperature measurements within the drying chamber indicated that the temperature within the chamber, even at region close to the nozzle, is closer to the outlet temperature. Hence, the outlet temperature was then used as an indicator in their report. It was speculated that in a larger spray dryer, the larger spread of the droplet evaporation region may enable better spatial resolution in measuring the wet bulb temperature at the nozzle region.

Vehring [16][34] proposed a predictive approach to provide an estimate of the time duration available for the drying of the droplet based on the initial evaporation rate of sprayed droplet at the wet bulb stage of evaporation corresponding to the inlet air conditions. Incorporating the use of the Peclet number (which denotes the rate of convective moisture loss relative to the internal diffusion rate of moisture), the time duration for surface enrichment of the initially dissolved solute to reach saturation can be further estimated.

As a quick digression from in-situ crystallization, it is noteworthy that the Peclet number concept has been widely used to characterize the particle formation process. Lin et al [35] defined the very initiation of drop changing as surface enrichment where the concentration of drop increases at the surface. Primary stages of solidification greatly affect the final morphology of the particle. Crust and shell formation can cause trapping of the solvent inside the particle. During the evaporation process thermal expansion could lead to bursting or tearing the solid particle. Increasing the solute concentration could generate solid dense particle. Although in this way crust formation initiates sooner, the thickness of the shell will be thicker resisting over rising inner pressure due to evaporation and thermal expansion [36]. Crust and shell formation process differ for various materials and solvent [35]. Tsapis et al explained the formation of particles could be characterized by Peclet number [37]. If one considers a drying time of τ_d, and particle radius of R, the diffusion coefficient D, the peclet number is defined

$$pe = \frac{R}{\tau_d D} \qquad (1)$$

According to Peclet number definition, it is the ratio of convection over diffusion. Then if the Peclet number is smaller than unity, the generated particles will be solid. Namely, the droplet have enough time to redistribute its deformation because the diffusion inside the particle is larger than evaporation of solvent. For the high peclet number the surface receding dominates diffusion inside the droplet. Then various conditions depending on a coat or shell is formed around the droplet affect the morphology. If a rigid shell, crust, is formed quickly, a solid hollow particle is generated and it doesn't buckle or wrinkle.

The quick crystallization predictive approach by Vehring has found applications in several particle engineering designs [32,38,39]. The approach was extended as a mechanistic approach to control the in-situ crystallization of leucine, a fast to crystallize material which is surface active, and the time duration available for crystal growth was estimated [40]. Prediction from this mechanistic approach was in agreement with the experimental results obtained, in which higher initial concentration of the leucine led to higher crystallinity of leucine; higher degree of crystallinity corresponding to a longer estimated time available for crystal growth. It was found that a threshold of ~ 20-25%wt initial concentration was required to achieve significant particle surface leucine crystallinity. Similar effect of the initial solid concentration on crystallization was also observed independently using a spray dryer of different scale [41]. Maa *et al.* [33] also found in their spray dried protein-mannitol formulation that 30%wt initial mannitol concentration was the threshold in which crystallization was induced. It is unclear at the moment on how applicable is this mechanistic predictive approach for slow to crystallize materials.

Nevertheless, the approach above suggests that the intermediate stage of drying, beyond the initial evaporation leading to saturation, could potentially be the crucial determining aspect controlling in-situ crystallization process. In similar veins, analysis on the drying history of relatively larger droplets indicated that the intermediate stage of drying, the "critical crystallization period", may be more significant in affecting the in-situ crystallization process [42]. The critical crystallization period occurs when the solidification of the droplet begins to significantly affect evaporation leading to the progressive increase in the droplet temperature. This finding was evaluated with both possible mechanisms for the in-situ crystallization process, the solid phase transition from amorphous solids and the supersaturation driven precipitation crystallization. This form of analysis is yet to be undertaken for fast to crystallize materials such as mannitol.

2.4 Potential use of counter current spray drying for crystallization control

On the premise of the potential impact of the manipulation of the intermediate stage of spray drying for crystallization control, there is a need for a spray drying technique, which will allow such manipulation. This led to further review on the potential application of the counter current spray drying configuration for crystallization control.

Published reports mainly focused on the co-current configuration of spray dryer. Only a few studies have been done on developing counter current dryer specifically in the food and pharmaceutical industries. Counter current spray dryer could have variety of configurations [1, 2]. The most common is to spray the feed material from the top, with a downwards direction of spray (Figure 2-1). The drying air is typically introduced from the bottom of the dryer with an upwards flow in order to utilize the entire volume of the chamber. This configuration was hypothesized to lend itself to crystallization control as the droplet initially contacts drying air of lower temperature and then progressively experience hotter drying air later on in its trajectory. Therefore, the wet bulb temperature of the solidification stage of the droplet may be extended giving more time for crystallization. Figure 2.1 illustrates the major differences in the drying history between co-current spray drying and counter current spray drying. Apart from the differences in the initial droplet-air contact, due to the counter current movement, forced convection is the dominant mode of heat and mass transfer throughout the entire trajectory of the particle. This is because of the opposed direction of feed injection and drying air providing velocity difference between the drying air and the particles. It is unclear if this will be useful to ‘enhance’ the intermediate drying stage of the particle.

Apart from that, the counter current effect in which the upwards moving air also provides drag resistance to the gravity induced falling particles giving relatively more residence time. Another possible advantage of the counter current approach is that as the droplet approaches the higher temperature air flow, the wet bulb temperature of the droplet also changes. As described and critically reviewed earlier, the wet bulb temperature may be an important parameter controlling the in-situ crystallization behaviour of particles within the spray dryer.

The counter current spray dryer, hitherto, is rarely used in the food and pharmaceutical industries. Published works showed that most of the available studies are related to the detergent industry in which very hot drying flow with high level of swirl are common drying conditions [43-49]. A common concern in using the counter current spray dryer is that it may be detrimental to heat sensitive materials; longer exposure to the hottest region of the dryer. This will have to be further evaluated as most degradation occurs when the particles is in the wet or semi-wet stage, as molecular mobility is a main factor contribution to degradation. In a counter current spray dryer, although the particles will progressively experience higher temperature towards the end of its trajectory, at that stage, the particles will actually be progressively drier. More work is required to further evaluate this aspect of counter current spray drying.

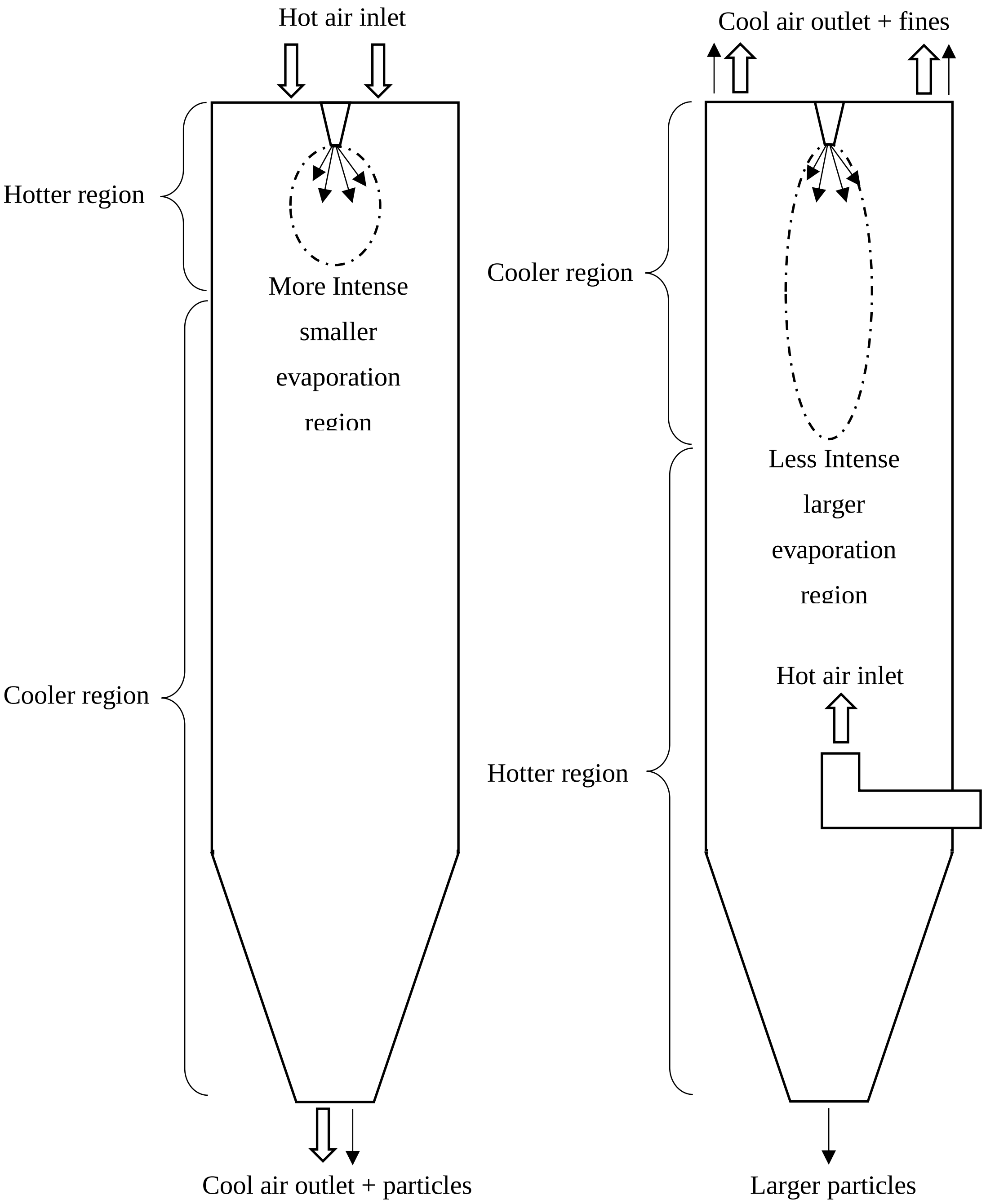

Figure 2-1 *Comparison between co-current and counter-current spray drying. A tall-form spray dryer is illustrated for a clearer illustration.*

Conclusion

Importance of crystallization in pharmaceutical manufacturing was reviewed with a focus on the morphology of excipients. Controlling morphology and stability of excipients influence efficacy of the active pharmaceutical ingredients. Spray drying as one of the key methods in production of controlled size particles could be used for manufacturing crystalline particles and excipients. Investigation in production of in-situ crystalline particle via spray dryer was initiated with Co-current dryer. In contrast, counter current spray-dryer which has high potential to be deployed for manufacturing crystalline particles rarely used specially in pharmaceutical manufacturing. Due to configuration of this type of dryer, sudden solvent evaporation does not occur immediately after atomization. Taking advantage of this characteristic along with higher residence time of particle provide appropriate features for producing crystalline particles.

In addition, theoretical studies around formation of crystalline particles requires more detailed attention. Very few studies focused on the formation of crystalline particles and morphology of them during quick evaporation. Therefore, prediction of particle crystallization needs combination of heat transfer mechanism with chemistry of crystallization.

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Chapter three

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3 Useful control strategy for in-situ crystallization of particles in a counter-current spray dryer[1]

Abstract

This paper evaluated the potential of counter current spray drying to produce crystalline particles in-situ, as a method to produce engineered particles. One main feature of the counter current spray dryer is the ability to induce a droplet drying history with progressively increasing drying rate; in contrast to a co-current spray dryer which particle immediately confronts high driving force of evaporation. In addition, counter current dryer provides higher residence time for particles. This work explored this unique feature of the counter current spray dryer to control the crystallinity of the particles formed within the drying chamber. Sucrose, lactose and mannitol were spray dried as model materials as they exhibit contrasting crystallization behaviour. The counter current spray dryer was suitable in producing well defined crystalline lactose particle. The lactose particle produced represented an agglomeration of fine thin lactose crystal. Surprisingly, the counter current spray drying with relatively lower initial evaporation rate resulted in amorphous mannitol particles. Fully crystalline mannitol was produced when the feed spray temperature was elevated. This may be an important strategy to control the crystallinity of mannitol particles particularly for pharmaceutical application. Similar feed pre-heating strategy in conjunction with counter current spray drying was used for sucrose drying. Crystalline sucrose was achieved with relatively lower drying temperature. This will be a valuable strategy for producing free flowing sucrose particles specifically for the food industry.

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[1] In-situ crystallization of particles in a counter-current spray dryer, Advanced Powder Technology 27 (6), 2299-2307

Keywords: counter current spray dryer, crystallization, particle engineering, mannitol, lactose, sucrose

Introduction

Crystalline particles in general exhibits lower tendency to agglomerate, cake and undergo phase change; hence, these features provide appropriate stability for such particles. Various methods for producing crystalline particles are available and each of them faces some drawbacks and advantages (Nokhodchi and Martin 2015). Batch crystallization with subsequent milling process is the most common method for producing crystalline particle (Midler Jr, Paul et al. 1994). Although advanced milling techniques are emerging, this process increases surface energy (generation of amorphous phase) of particles which decreases the free flowing behaviour of particles(Chow, Tong et al. 2007). Utilization of the anti-solvent method facilitates production of engineered crystalline particles but flammability of anti-solvent significantly limits its application particularly in larger scales (Kaialy and Nokhodchi 2013, Kho and Hadinoto 2013). Spray drying is a well-known method for producing engineered amorphous particles. There are reports on the production of amorphous particles in spray drying and followed by subsequent treatment to induce phase transition for generating crystal particle is a traditional method. During this phase transition the moisture content of the particle may contribute to particles stickiness; subsequently, large chunk particles are produced which reduces free flowing ability of the particles (Bronlund and Paterson 2004, Woo, Fu et al. 2012). But the main advantage of spray drying process is the flexibility of this method on controlling the appropriate particle size in single stage without further treatment like milling (Healy, Amaro et al. 2014).

In situ crystallization in spray drying is a new method of producing engineered crystalline particles. Although crystallization occurs randomly for the particles through drying, this method was scientifically investigated by Shastry et al for producing crystal sucrose by a continuous drying method of 50µm sucrose stream (Shastry and Hartel 1996). They proved that with change in the drying process crystals can be produced in a continuous manner. Chio and Langrish utilized potential of a one-step crystallization approach and employed spray drying for producing partially the crystalline lactose particle (Chiou and Langrish 2008, Chiou, Langrish et al. 2008). Complementary research was carried out on single droplet(Fu, Woo et al. 2012, Woo, Fu et al. 2012) and lab scale spray dryer (Chiou, Langrish et al. 2008, Islam and Langrish 2010, Islam, Langrish et al. 2010) which proved that some degree of crystallinity is feasible to be achieved by this method.

The challenge of crystalline particles formation is the relatively long time scale nature of crystallization (Myerson 2002). In contrary, spray drying is a fast drying method in which most of the moisture is evaporated in less than a second. In addition, residence time of particle in the dryer is in the order of seconds which further hinders crystallization. To overcome these features one possible approach is to reduce the evaporation rate to avoid early particle formation giving more time for crystallization before the particle solidify; however, formation of slightly non-dried particles may be ensured. The threshold between the formation of amorphous and crystalline particle is very narrow (Bhandari, Datta et al. 1997, Langrish and Wang 2009). On this basis production of engineered crystalline particle necessitates the understanding and control of the mechanism of heat and mass transfer affecting the crystal formation. In other words, it is important to control the heat and mass transfer to ensure the required time for crystallization but yet produce sufficient drying.

In typical co-current spray dryer, droplets reaches terminal velocity very rapidly after injection. Therefore, the drying air dominates the particle movement and will subsequently affect residence time of particle in the dryer(Zbicinski, Strumillo et al. 2002, Wu, Patel et al. 2007). Hence, effectively diffusion is the main mode of heat and mass transfer and air temperature decreases as droplet travels to the outlet. In such a situation, high temperature is required at the inlet to compensate the temperature reduction due to evaporation. Increasing the drying temperature contributes to early crust formation and is one of the key factors that would hinder crystal formation (fig 3.1). Most spray drying in-situ crystallization works reported for co-current dryer. In a counter current dryer the inverse direction of drying air amplifies the rate of heat transfer as forced convection is the dominant mode of drying and there is always a difference in the opposing velocity between the particles and drying air. In addition, the drag force is against gravitational force and resists droplet falling which can provide higher residence time, shown in fig 3.1. This can potentially allow the decrement of the maximum drying temperature. It is the hypothesis of this work that these factors provide the condition suitable for crystallization (Sedelmayer, Griesing et al. 2013). There is limited published research on the effect of different drying history in a counter current spray dryer which would affect crystallization process. On this basis, this research intent to investigate effect of the counter current in providing a different mechanism of heat transfer and longer residence time on improving in situ crystallization for production of crystalline particles.

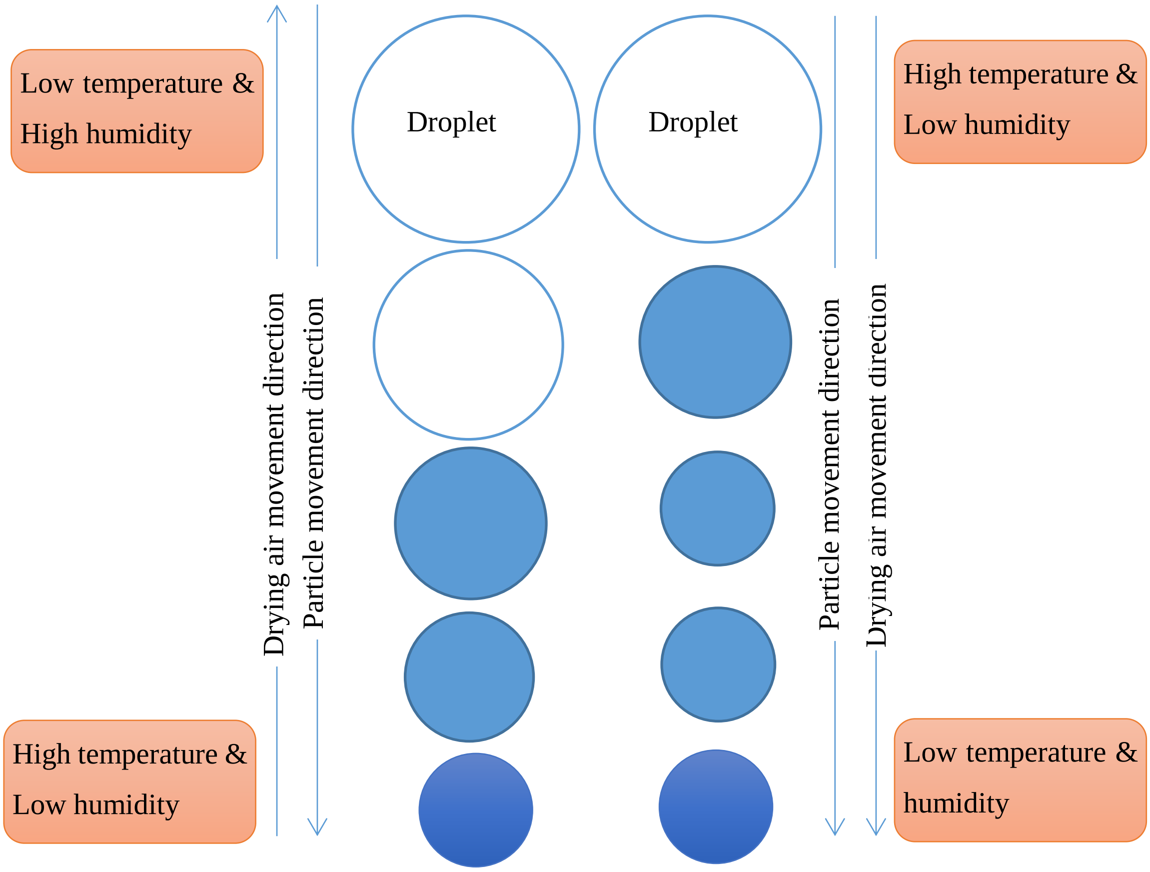

***Figure 3-1**. comparison of particle drying history: left)counter current right) co-current spray dryer*

3.1.1 Solution preparation

Three types of sugars including sucrose, lactose and mannitol that are mainly used in pharmaceutical and food industry were selected. Lactose and mannitol are two main materials employed in inhaler as carrier particles and their characteristics play critical role in efficacy of drug delivery (Maltesen and van de Weert 2008). Lactose largely has been utilized in the pharmaceutical without any toxicity reported. Albeit mannitol has less widely used in the pharmaceutics, its physicochemical properties facilitates mannitol handling and manipulation(Chow, Tong et al. 2007). The other criterion for selection of these materials was based on the difficulty in crystallization and drying. Mannitol has a very low glass transition temperature which allows crystallization. In turn, sucrose is very difficult in drying and crystallization particularly because of high degree of stickiness and viscosity which hinder drying. Lactose has a high glass transition in comparison with other sugars. Although sucrose is not used as a carrier particle, the similarity and dissimilarity of this sugar to mannitol and lactose provide us a better understanding of the mechanism of in-situ crystallization. For consistency, all the solutes were prepared in 10% mass concentration to reduce number of variables affecting drying. Solute was prepared with distilled water in ambient temperature and stirred for 60 minutes to ensure feed is totally dissolved. Only lactose solute was stirred for at least 4 hours to ensure an equilibrium of α and β has been achieved (Fu, Woo et al. 2012).

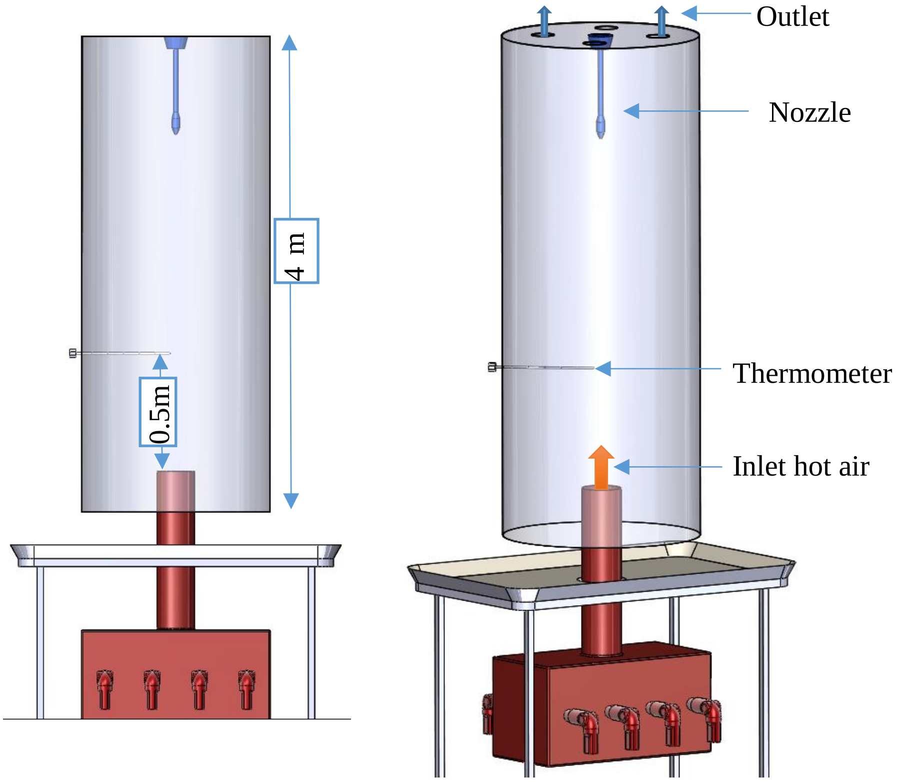

Figure 3-2. *schematic of counter current spray dryer developed in Monash university*

Materials and equipment

3.1.2 Experimental equipment

A counter current tower developed in the department of chemical engineering of Monash University was used in this work (Fig 3.2). The tower height was 4 meters with diameter of 60 cm which was open at the bottom. Liquid feed was pressurized by compressed air and injected with a pressure atomizer from the top of the tower. Two different nozzles (Amfog nozzles Red O-ring and Black O-ring) were deployed for generating different droplet sizes. The feed flow rate differed for the nozzles in the same pressure, Red O-ring 1.2 liter/hr and Black O-ring 2 lit/hr at 6bar pressure. Drying air was generated with the aid of 8 adjustable heat-guns which was mixed with compressed air for controlling flowrate and temperature. Drying air inlet was centred on the tower bottom where the drying air was entrained with the ambient flow inside the tower and rises up to the top of the tower. Tower and hot air generator were covered with glass wool to reduce heat loss through the walls. Temperature was measured at three different steps through the tower, at drying air inlet, at lower half of the tower where drying air quite developed and at the tower outlet. Generated particles deposited on a tray installed at the bottom of the tower and allowed manual collection of powders. The time for stabilization of tower at the beginning of the tests was 25 minutes to achieve steady state.

3.1.2.1 Droplet measurement

Droplet size distribution is a critical factor in spray drying; hence, this parameter was measured for the nozzles employed in this study. High speed photography with backlight illumination measurement technique was used. Fig 3.3 depicts the method developed for droplet measurement. In order to achieve quality measurement, it was important to capture droplets only on the plane of focus of camera. Generation of large amount of droplets by spray cone is a limitation for photography which makes the photo blurred. Therefore, in this experiment a setup was developed to filter a narrow layer of droplets to the plane of focus of the camera. In order to ensure variety range of droplets are captured, the nozzle was placed in different position on the rig. The filtered droplets , fig 3.3, are representative of whole spray as the spray cone is symmetrical and the slit that filter droplets is wide enough to pass droplets from the centre of the spray to the edge of the spray. As droplets moves fast, a high speed camera (Nikon 8000f/s with a Af60 Nikkor micro lense) was required to freeze the droplet motion. In addition, light frequency is an issue which would contributes to dark images. High intensity DC LED (30 watts), was used to provide continuous illumination and high contrast between the background and the droplets. Image processing for the size calculation of the droplets was accomplished by using ImageJ. The image size distribution is based on measurement of more than 1000 droplets.

3.1.2.2 Analytical tests

Scanning electron microscopy and light microscopy are the fastest methods for early observation of particle characteristics. In this study a FEI Nova Nano SEM 450, a Phenom benchtop SEM and a light microscope with magnifications of 1 million X, 20KX and 10 X respectively were used for particle observation. XRD method was used to recognize crystalline peaks as the main characteristics of crystalline materials. The XRD machine was Riguka Miniflex capable of analysing six samples. To avoid phase change of particles after production, they were stored in a desiccator and XRD analysis was carried out on the day of production. XRD analysis was carried out in the range of 0° to 40° as the main picks of the materials of this study can be observed in this range. The speed of scanning was set on 2°/sec providing enough accuracy for the results. Also, analysing the XRD results was carried out by an open source software, MAUD, to filter the available noise in the raw data.

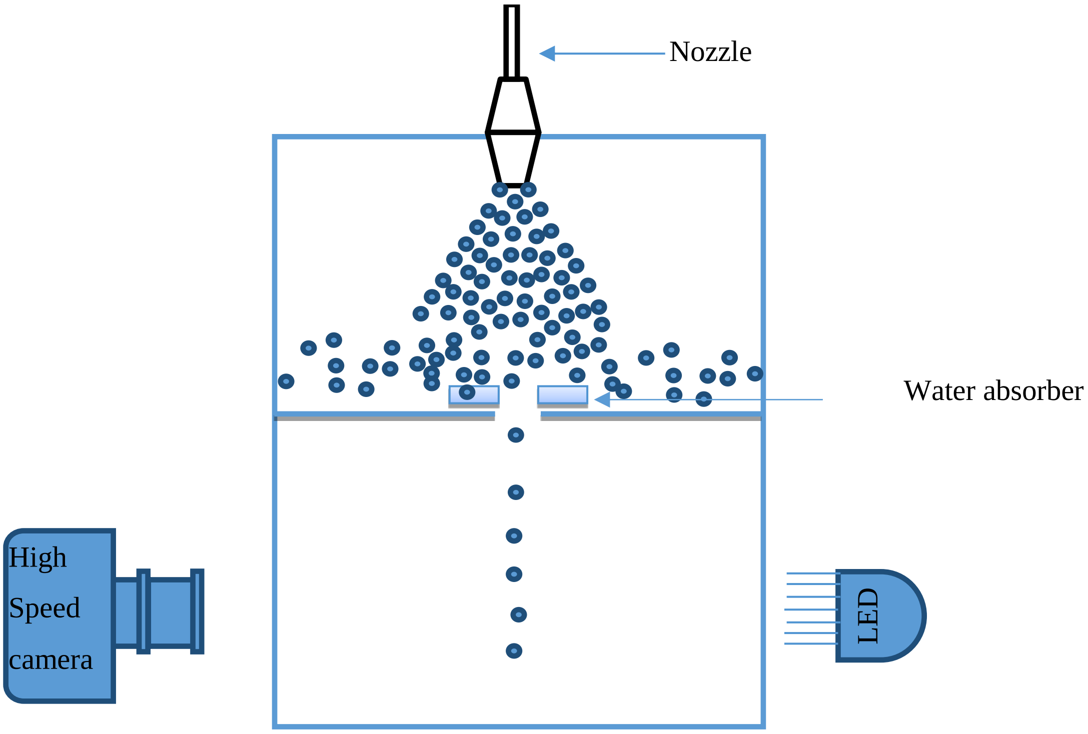

Figure 3-3. *Schematic of setup developed for the backlight photography of thin layer of droplets*

Results

3.1.3 Sucrose

Sucrose is notorious for its difficulty to spray dry because of the stickiness which mostly emanates from its viscosity. Extensive range of flowrate and temperature was studied to explore the drying characteristics and possible in-situ crystallization of sucrose which is tabulated for range of temperature and flow rate in Table 3.1. The experimental runs in table 3.1 is the collated summary of the whole set of experiments which is presented in the appendix (table 3.A1). Evaluation was firstly undertaken for smallest range of droplet size which can be produced in the spray drying setup, average droplet size of about 50 micron. This would represent the higher residence time available within the spray chamber (within the range of experiments) to induce any possible crystallization during the dehydration process. The estimated residence time, using the air velocity at the outlet and the perfect shrinkage particle size, would be 5-6 s.

Result for small size droplet, 50 µm, showed in the low temperature of 65°C, runs 1-Table 3.1, sticky particles was obtained indicating insufficient drying. Increasing the temperature to the range of 75°-95°C remarkably decreased the stickiness of particles (runs 2-Table 3.1). It is noteworthy that run2 in Table1 represent a collation of multiple experiments (full information in Table 3-A1). Electron microscopy of these particles in fig 3.1 showed they are spherical amorphous particles resembling amorphous particles reported in the literature. In order to postpone particle solidification the drying air flow rate was slightly reduced but it resulted in sticky particles again, Run3- Table 3.1. The results showed that the range of velocity variation utilized didn't affect drying process directly, but it may result in drag force raise and subsequently increases the residence time of the particle. Experiments were repeated for the aforementioned range of temperature in higher ambient humidity which resulted in sticky particles, Run4-Table 3.1. Interestingly, this experiment was carried out in very low drying temperature, but variation in the ambient humidity, around 50%, significantly affected drying process in this range of temperature. Sticky particles was produced particle possibly due to reduction of evaporation or high moisture absorptivity of these particles in contact with highly humid environment at the end of process.

These results showed that even for the relatively higher residence time with the smallest droplet size available it was not sufficient to induce crystallization. By increasing the drying temperature the elevated drying rate could only dehydrate the droplet and did not provide sufficient time for crystallization to occur, Row 5-Table 3.1. This could be due to the small size of the droplet which dehydrates relatively fast. This shows that even if the residence time is long, the effective residence time available for particle crystallization has to be manipulated.

Therefore, the experiments were repeated with the larger droplet size by changing the nozzle size. In using the larger nozzle, inevitably the flow rate of the spray was also increased which would have led to larger amount of evaporation leading to cooler outlet air. It was of the intention that in addition to the larger droplets generated, the cooler and the more humid air will provide evaporation giving more 'wet' time for effective in-situ crystallization. As the droplet size was increased, row 6 table 3.1, a combination of sticky particles and crystalline was observed. However, most of the particles exhibited the typical round amorphous morphology. This observation complied with the concept of sticky-point developed by Ozman and Langrish that increasing drying temperature would results in sticky particles (Ozmen and Langrish 2003).

The runs with the larger droplets were indications delineating the need to preserve the wetness of the droplet during the spray drying process. Ideally, lower drying temperature should be used. However, for sucrose to crystallize, it will be useful to quickly form the particles or if precipitation based crystallization were to occur, a very high supersaturation needs to be induced. We further investigated one possible approach to achieve this by heating up the sucrose solution feeding into the spray. It was deduced that the higher feed temperature will induce very quick evaporation followed by lower temperature convective dehydrations. This strategy draws inspiration from flash drying in which feed is heated up to the boiling point and then injected resulting in fast evaporation and very early crust formation (Mujumdar 2014). This method is recommended for non-heat sensitive materials. In employing this idea the temperature of feed just was increased at most to 75°C; namely below boiling point of the feed.

Table 3-1. *Spray dried sucrose in various processing conditions*

	Average Droplet size(µm)	Ambient humidity	Average inlet temperature range °C	Velocity m/s	Feed Temperature °C	Results
1	50	35%	65	0.33	22	Sticky
2	50	35%	75-95	0.29-0.31	22	Non sticky
3	50	35%	90-98	0.25-0.27	22	Sticky
4	50	80%	76-90	0.31	22	Sticky
5	50	40%	115	0.31	75	Non Sticky
6	80	40%	120	0.32-0.34	22	Sticky
7	80	35%	65-80	0.28	75	Non sticky, many small crystalline
8	80	40%	110	0.32	75	Non sticky,

- In this paper "sticky" refers to particles which are not free flowing and thus could not be easily collected from the deposit tray

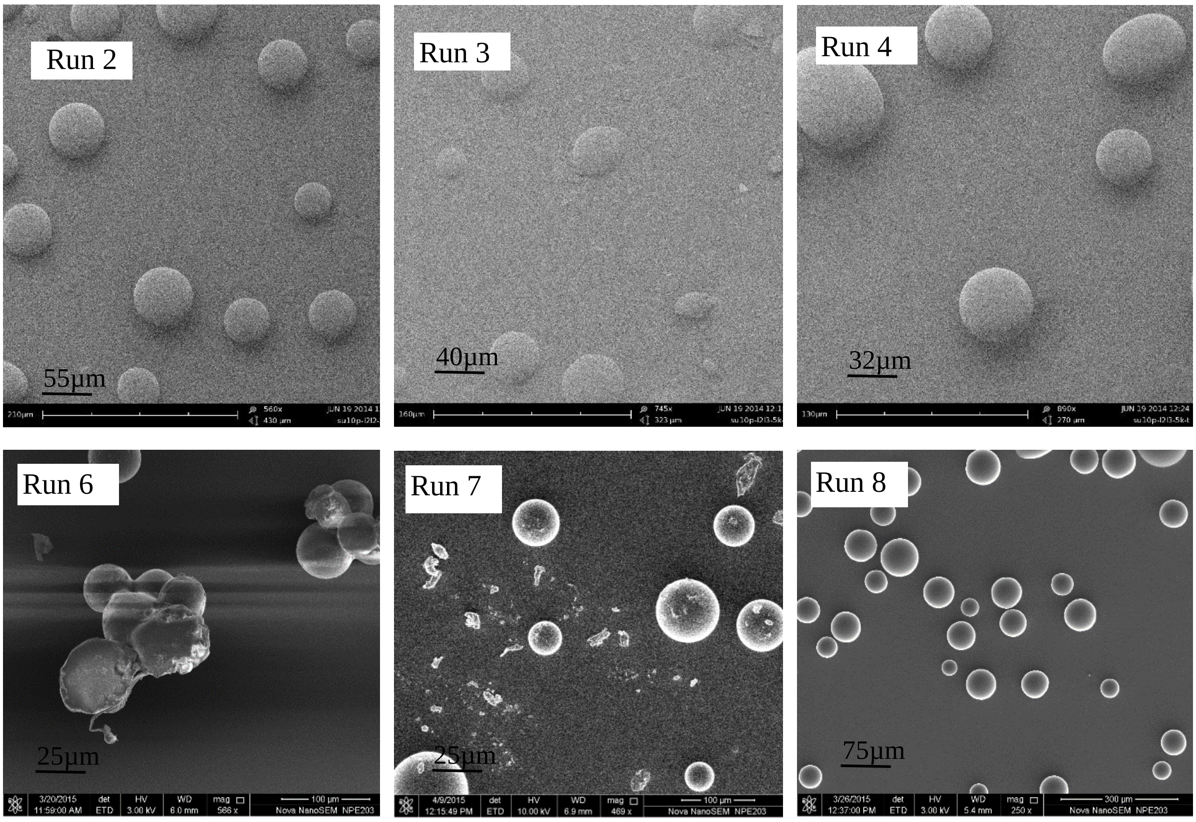

Figure 3-4. *SEM and light microscopy images of sucrose particles generated in various processing conditions according to table 1.*

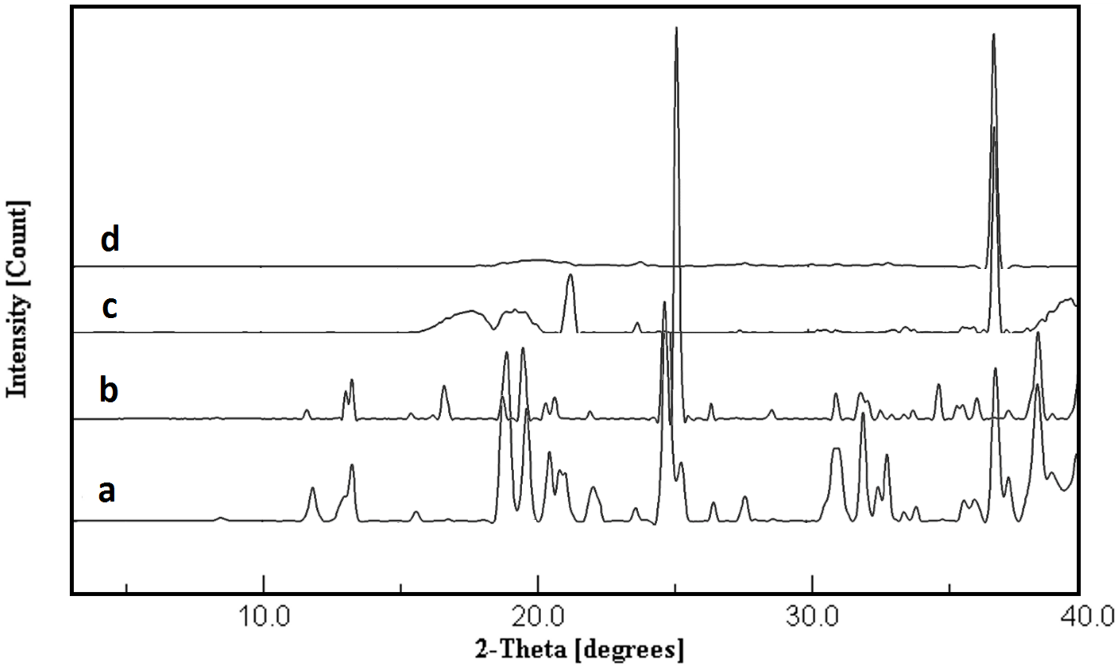

Figure 3-5. *XRD spectrum for spray dried sucrose (droplet 80µm) a) purchased unprocessed sucrose, b) Run 7: spray dried at 80°C with feed of 75°C, c) Run 8 : spray dried at 110°C with feed of 75°C, d) Run 6: spray dried at 80°C with feed of 22°C*

The next series of experiment was carried out with a nozzle with median droplet size of 80 µm which also produced higher flow rate, Run 7-Table 3.1. For this reason, the drying flow rate was increased but the drying temperature was almost fixed in the previous range. The results showed the increasing feed temperature improves the crystallinity of sucrose particles. Feed temperature of 75°C along with drying air of 65°C generated particle with negligible stickiness but still round amorphous particles. Increasing drying temperature to 80°C reduced stickiness of the particles while many tiny crystalline particles were produced. As expected, increasing the drying air temperature above 100°C along with elevated feed temperature reduced the particle wet time and led to amorphous particles, Run 8- Table 3.1. SEM images for run 7, fig 3.4, clearly shows the average size of crystalline particle is smaller than the amorphous particles. The XRD result for the mentioned condition, fig 3.5.b, confirmed the existence of crystalline particle as the main peaks for sucrose crystal can be observed. Complementing the SEM, the XRD scan showed that increasing the drying temperature resulted in reducing crystallinity (fig 3.5.c). Similar trend can be distinguished for drying without elevated feed temperature, fig 3.3.b, where there was no crystalline peaks observed.

3.1.4 Lactose

The same set of strategy was evaluated for lactose. Similarly in low temperature drying temperature particles were a little sticky but increment in the drying temperature to above 85°C resulted in thoroughly dried particles (run 1-2- table 3.2). Increasing temperature to 120°C did not affect the crystallization and all particles were amorphous (run 3-Table 3.2). In the attempt to increase the effective 'wet' time available for in-situ crystallization, the experiments were repeated with the 80 μm droplet size, runs 5-6, which was also associated with higher spray rate. Results showed in the low temperature drying, below 80°C, particles are totally amorphous but the interesting results were observed with increasing temperature above 85°C where the crystallinity of particles was increased. Result of X-ray crystallography, fig 3.4, represented that the material has the main peaks of polymorphous lactose especially in 10.4° for β lactose and at 12.4° and 16.5 ° for lactose.

Therefore, increasing the droplet size which increases the effective 'wet' time rather than the residence time also worked for lactose in inducing in-situ crystallization. A unique trend observed for lactose which may be contradictory to the deduction above that higher drying temperature was required to induce crystallization in the 80 micron droplets (Leong 1987). While the usage of larger droplets and spray rates induces a longer 'wet' time, a higher drying temperature, in contrast will have the tendency to induce a shorter 'wet' time due to the higher dehydration rate. Additional explorations were then undertaken by manipulating the temperature of the feed solution.

This processing condition was repeated with the larger droplets of 80μm, runs 7-8. Surprisingly, in the low drying temperature crystalline peak was observed in XRD results. These peaks were not as distinct as the high temperature drying runs in the earlier experiment, but despite the high temperature drying in which polymorphous peaks were observed, in this test the short peaks for α lactose especially at 12.4° was very obvious.

Similar to sucrose, the strategy successfully produced partially crystalline lactose particles.

Table 3-2. *Comparison of lactose crystallinity due to change of processing condition in Spray dryer*

	Average Droplet size(μm)	temperature	Velocity m/s	Feed Temperature	Results
1	50	65	0.27	22	Sticky
2	50	85	0.31	22	Sticky
3	50	120	0.33	22	Non Sticky
4	50	106	0.31	75	Non-sticky
5	80	80	0.31	22	Non sticky
6	80	105	0.31	75	Partially crystalline
7	80	85	0.29	75	Partially crystalline
8	80	105	0.32	22	High degree of crystallinity

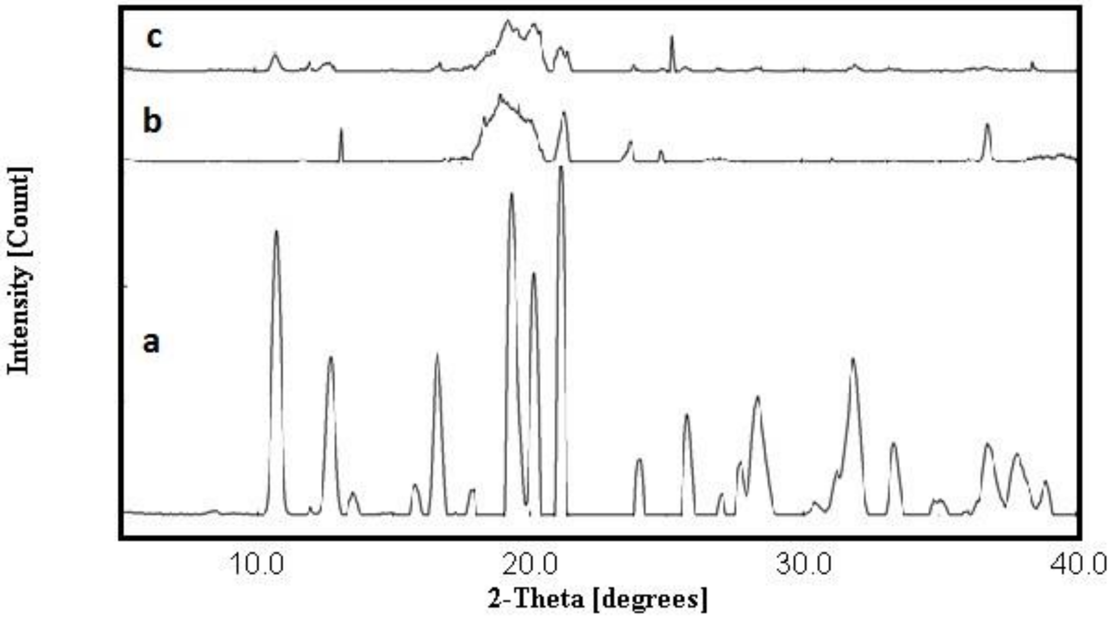

Figure 3-6. *XRD result for lactose produced in different processing condition a) Run 8: : spray dried at 105°C with feed of 22°C, b) Run 6:spray dried at 105°C with feed of 75°C 6, c) Run 7: : spray dried at 85°C with feed of 75°C*

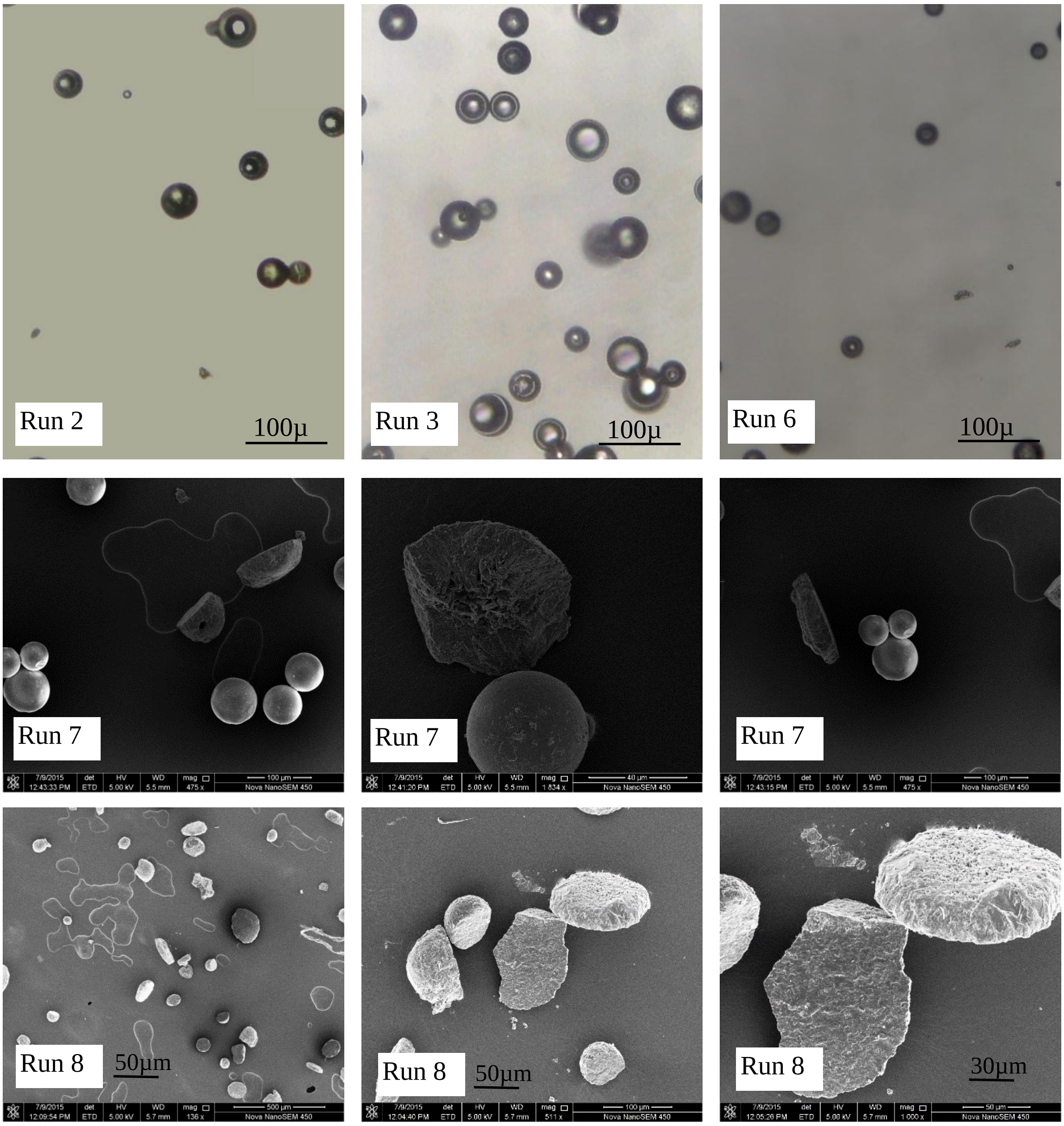

Figure 3-7.*SEM and light microscopy images of lactose particles generated in various processing conditions according to table 3.2*

3.1.5 Mannitol

The strategy developed from the two difficult-to-crystallize materials (sucrose and lactose) was then evaluated for mannitol which is easy to crystallize. The low glass temperature and low stickiness of mannitol put it among the materials conveniently spray dried. Currently mannitol has come to centre of focus as an alternative to lactose specifically as a carrier material in inhalers. Mannitol structure consist of elongated molecules and this structure can be found in the large particles of mannitol in which elongated tiny crystal stick together and formed large particle.

With minimal tests on this material, increasing the droplet size and spray rate did not produce significantly crystalline particles. Even with the larger spray rate and average droplet sizes, increasing the drying temperature did not result in significant crystallization (Run 1-2 Table 3.3). This was evident by the agglomeration and non free-flowing behaviour of powder produced by these runs during particle collection. Even at the elevated temperature (Run 3 Table 3.3), the XRD analysis showed an amorphous like pattern (Fig 3.9-d). Despite lactose which crystalline particle was observe with increasing drying temperature, this factor merely didn't affect mannitol crystallization, Run4-Table 3.3. Even though the particles were free flowing on the deposit tray, the XRD result in fig 3.9.c showed almost no peak for crystalline lactose and the result shows amorphous like pattern.

Interestingly, raising the feed temperature significantly along with high drying temperature affected crystallization of mannitol, Run 5 Table 3.3. The collected particles were very free flowing behaviour and no agglomeration during particle collection was observed. The SEM image, fig 3.10, of this result clearly represent crystalline structure of mannitol particle produced with this strategy. The XRD data in fig 3.9.a confirmed high degree of crystallinity where very sharp peaks can be observed for this processing condition. The peaks for this yield resemble the peaks for the purchased unprocessed crystalline D-mannitol and follows similar peaks.

Table 3-3. *Comparison of Mannitol crystallinity due to change of processing condition in Spray dryer*

	Average Droplet size(μm)	Average temperature	Velocity m/s	Feed Temp	Results
1	50	75	0.27	22	Sticky
2	80	75	0.27	22	Sticky
3	80	80	0.31	75	Non-sticky
4	80	115	0.33	22	Non sticky
5	80	110	0.33	75	Non sticky with elongated crystal

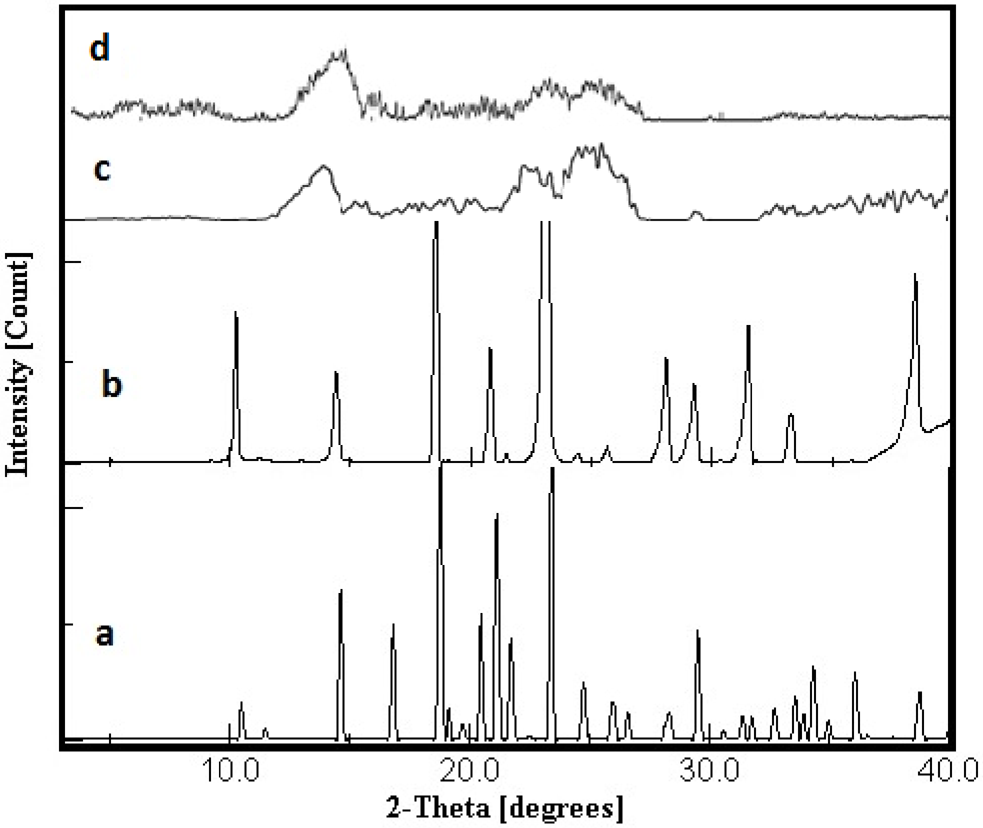

Figure 3-8. *XRD result of mannitol: a) Run5 :spray dried at 110°C with feed of 75°C b) purchased unprocessed D-mannitol c) Run3: spray dried at 80°C with feed of 75°C, d) Run4: spray dried at 115°C with feed of 22°C*

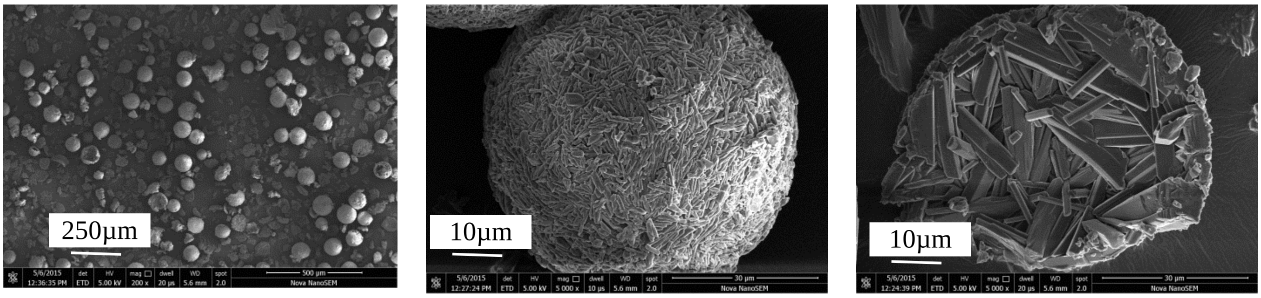

Figure 3-9. *Mannitol spray dried in elevated feed temperature, Run 5: spray dried at 110°C with feed of 75°C*

Discussion

In the typical co-current spray drying configuration, the sprayed droplets will tend to firstly experience relatively hotter air at the initial droplet-air contact followed by relatively cooler air as it travels with the convective air flow. This implies that the evaporation is very rapid at the initial droplet-air contact with subsequently decreasing driving force for evaporation; from the decreasing air temperature and the decreasing moisture content in the particle. In contrast, in the counter current configuration, the droplet experiences relatively lower temperature at the initial droplet-air contact followed by progressively increasing temperature. Therefore, the droplet may experience an increasing rate of dehydration; although the progressively decreasing moisture content in the particle may augment this dehydration process (Piatkowski and Zbicinski 2006, Wawrzyniak, Podyma et al. 2012). This difference in particle drying history significantly affected the particle formation behaviour of the particles.

For mannitol, the counter current drying history produced amorphous particles. This was a surprising result as most reports in the literature reported the spray drying of well crystalline mannitol particles (Littringer, Paus et al. 2013). Therefore, this suggests that to produce crystalline spray a dried mannitol particle, a rapid initial dehydration is required to induce the formation of the individual mannitol crystals in the forming particle. This is further supported by further experimental evidence when the temperature of the feed was increased which would have enhanced the initial evaporation of the droplet. It is noteworthy that the effect of the inlet feed temperature on the in-situ crystallization behaviour of spray dried particles have yet to be reported in detail in the literature. Manipulation of this parameter may be important for a co-current spray dryer in producing such easy to crystallize particles.

For slower to crystallize materials such as lactose, on the other hand, the slower initial dehydration followed by progressively higher dehydration was observed to be suitable in producing in-situ crystallized lactose particles. The benefit of the slower initial dehydration rate is further illustrated when the inlet feed temperature was increased (expected to increase the evaporation rate) which decreased the formation of the crystallinity in the particle. It is supposed that the increased feed temperature may have caused excessive initial evaporation rate leading to rapid formation of amorphous lactose solids.

A previous report also noted the need for relative high air temperature to induce in-situ crystallization once the particle is formed (Chiou, Langrish et al. 2008). The reasoning provided indicated the high temperature was required to overcome the glass transition barrier to allow solid phased transition from amorphous to form partially crystalline solids. This was also observed in the current work. Even with a slow initial evaporation followed by a rapid evaporation strategy, high counter current inlet air temperature was required. However, the effect of the inlet feed temperature discussed earlier suggests that the in-situ crystallization process may not be solely controlled by the hot air conditions in the latter part of dehydration; the solid phase transition process. The initial solid formation phase of the droplet, which may have been affected by the inlet feed temperature, may also play an important role in controlling the in-situ particle crystallization process. This will be an important aspect for further investigation and is currently in progress. Although direct comparison could not be made, compared to past reports on using a co-current system, relatively lower temperature of 110°C was sufficient for the counter current system (the former required at least 180°C inlet air temperature). It was unclear at the moment if the lower required temperature was due to the larger residence time available or predominantly due to the counter current effect with progressively increasing air temperature.

Relative to lactose and mannitol, sucrose particle did not produce such high crystallinity. It is noteworthy that between the materials evaluated, sucrose has the lowest propensity to crystallize. The slow initial dehydration followed by progressive dehydration which worked for lactose in inducing in-situ crystallization was not successful for sucrose. Nevertheless, for sucrose, the effect of the inlet feed temperature on the in-situ crystallization process was observed. Under the elevated feed temperature, however, relatively lower counter current air temperature can be used. This observation is in agreement with the Leong experiment that a material with solubility considerably independent of temperature has crystallization independent of drying air temperature (Leong 1987). For such a low propensity to crystallize material, in the context of spray drying, a different mechanism or strategy may be required to elucidate the experimental trend observed. This will be the subject of our future work.
One may argue how drying kinetic is affected by crystallization. Crystallization is affected by drying kinetics with changing in evaporation time, providing various moisture contents drying temperature etc. Opposed to drying kinetics, effect of crystallization on drying kinetics of the materials that were experimented in this study was inferior.

Conclusion

The effect of droplet/particle residence time and the effective ‘wet’ residence time on the in-situ crystallization process of sucrose, lactose and mannitol were evaluated. It was found that preserving the effective ‘wet’ time was essential in allowing in-situ crystallization of the particles. This was undertaken by using droplet of larger average sizes and increasing the spray rate of the feed. Additional experiments showed that the manipulation of the inlet feed spray temperature significantly affected the in-situ crystallization process as it affects the initial particle formation process; particularly for mannitol and lactose. Further analysis revealed that high initial evaporation is required for the in-situ crystallization of mannitol. On the other hand, lactose in-situ crystallization requires a slower initial evaporation rate. These showed that the initial particle formation process may be another mechanism controlling the in-situ crystallization of rapidly formed particles in spray drying in addition to the solid phase mechanism reported in the literature. These analyses were possible due to the counter current configuration in which a droplet typically experiences a slower initial dehydration rate followed by a higher temperature drying process as it approaches the counter current air inlet. More work is currently underway to investigate the significance of the initial particle formation phase in controlling the in-situ crystallization of particles in spray drying.

Appendix

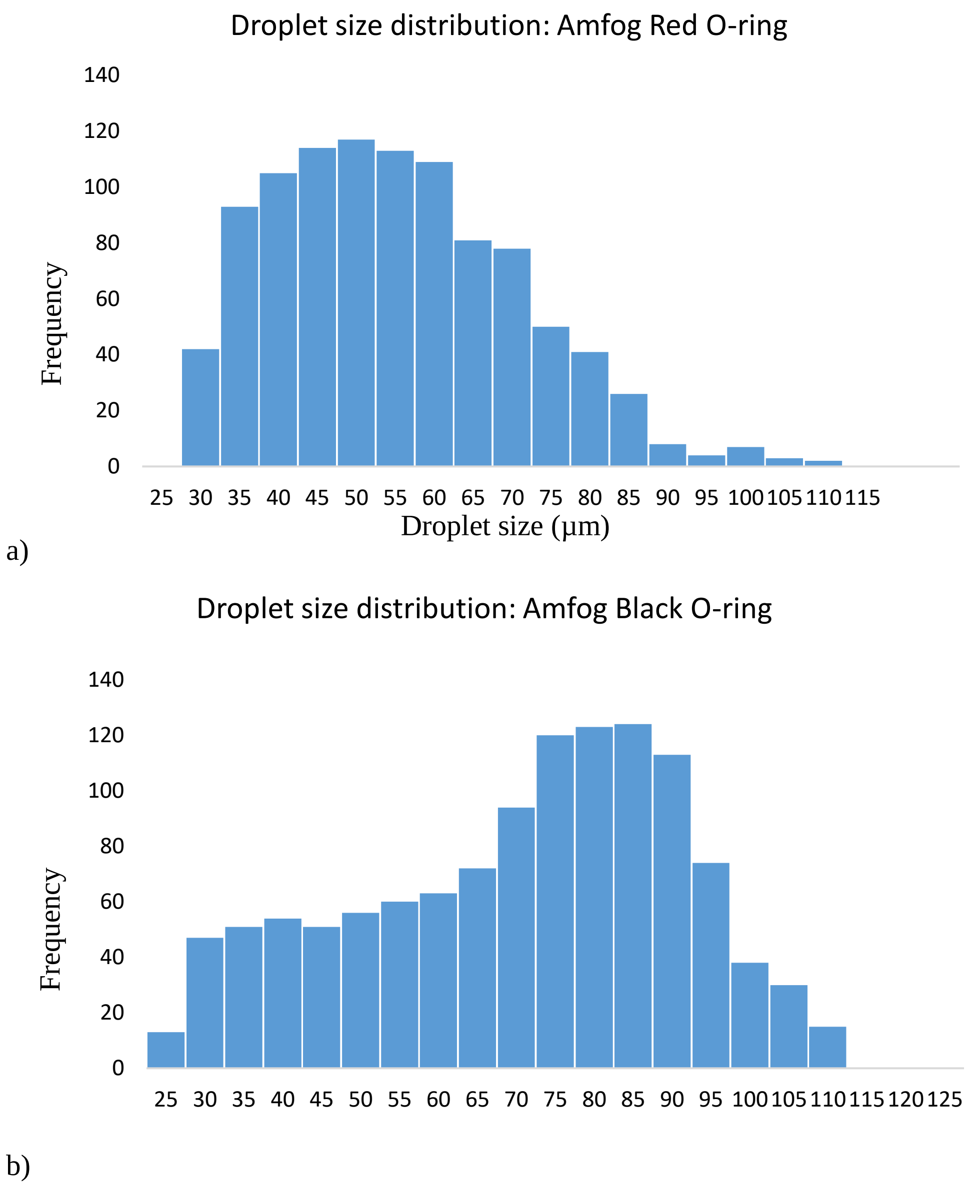

Figure 3-10A. *droplet size distribution for smaller orifice nozzle (Red O-ring), b) droplet size distribution for larger nozzle (Black O-ring)*

***Table 3-4A**. Spray dried sucrose in various processing conditions*

	Average Droplet size(μm)	Ambient humidity	Average temperature	Velocity m/s	Feed Temp	Results
1	50	35%	65	0.33	22	Sticky
2	50	35%	75	0.31	22	Non sticky
3	50	35%	90	0.31	22	Non sticky
4	50	35%	93	0.31	22	Non sticky
5	50	35%	95	0.29	22	Non sticky
6	50	35%	98	0.25	22	Sticky
7	50	40%	95	0.27	22	Sticky
8	50	80%	90	0.31	22	Sticky
9	50	80%	76	0.31	22	Sticky
10	50	40%	115	0.26	75	Non sticky
11	80	40%	120	0.32	22	Sticky and some tiny crystalline
12	100	40%	120	0.34	22	Sticky
13	80	40%	110	0.32	75	Non sticky, particles with large holes
14	80	35%	63	0.28	60	sticky
15	80	35%	63	0.28	75	Non sticky, caking
16	80	35%	80	0.28	75	spherical particles and small crystalline

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Link to next Chapter

In the previous chapter, it was found that it was possible to produce in-situ crystalline particle via counter current dryer by the adjustment of the drying air temperature and flow rate, droplet size and feed temperature. From the experiments, it was found that the dehydrating air humidity within the chamber is a parameter which undermines the other operating conditions evaluated. This parameter was also reported to be influential in enhancing in-situ crystallization in co-current spray dryer. What is the exact role of air humidity in in-situ crystallization control? How does increased or decreased air humidity impacts the drying history of the droplet leading to different crystallinity? Therefore, the next chapter aimed to unveil the effect of the humidity and understand the mechanism in which humidity affects the degree of crystallization in spray dried particles.

Chapter four

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4 The role of the intermediate stage of drying on particle in-situ crystallization in spray dryers[2]

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% 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

Introduction

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[2] The role of the intermediate stage of drying on particle in-situ crystallization in spray dryers, Powder Technology 323, 357-366

The control of particle crystallinity of pharmaceutical sugars through the spray drying process has recently attracted significant attention (Woo, Lee et al. 2016). 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 (Vehring, Foss et al. 2007); 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(Costantino, Andya et al. 1998, Vehring, Foss et al. 2007). Amorphous particles may be relatively stable where a sufficiently low humidity is maintained during storage (Abdul-Fattah, Truong-Le et al. 2007). The crystalline state may also offer better dispersibility of particles(Lucas, Anderson et al. 1999, Chew and Chan 2002, Wong, Kwok et al. 2014). 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)(Littringer, Mescher et al. 2012, Woo, Lee et al. 2016, Lin, Woo et al. 2017). 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(Woo, Lee et al. 2016). Some materials are slow to crystallize e.g. lactose. These materials have a crystallization time scale order longer than the particle formation time scale (McSweeney and Fox 2009). 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 (Chiou and Langrish 2008, Woo, Daud et al. 2008, Islam, Langrish et al. 2010). For such materials, there are several approaches reported to increase the crystallinity of the formed particle, by processing parameter manipulation(Chiou, Langrish et al. 2008, Langrish and Wang 2009, Islam, Langrish et al. 2010, Das and Langrish 2012, Shakiba, Mansouri et al. 2015, Shakiba, Mansouri et al. 2016).

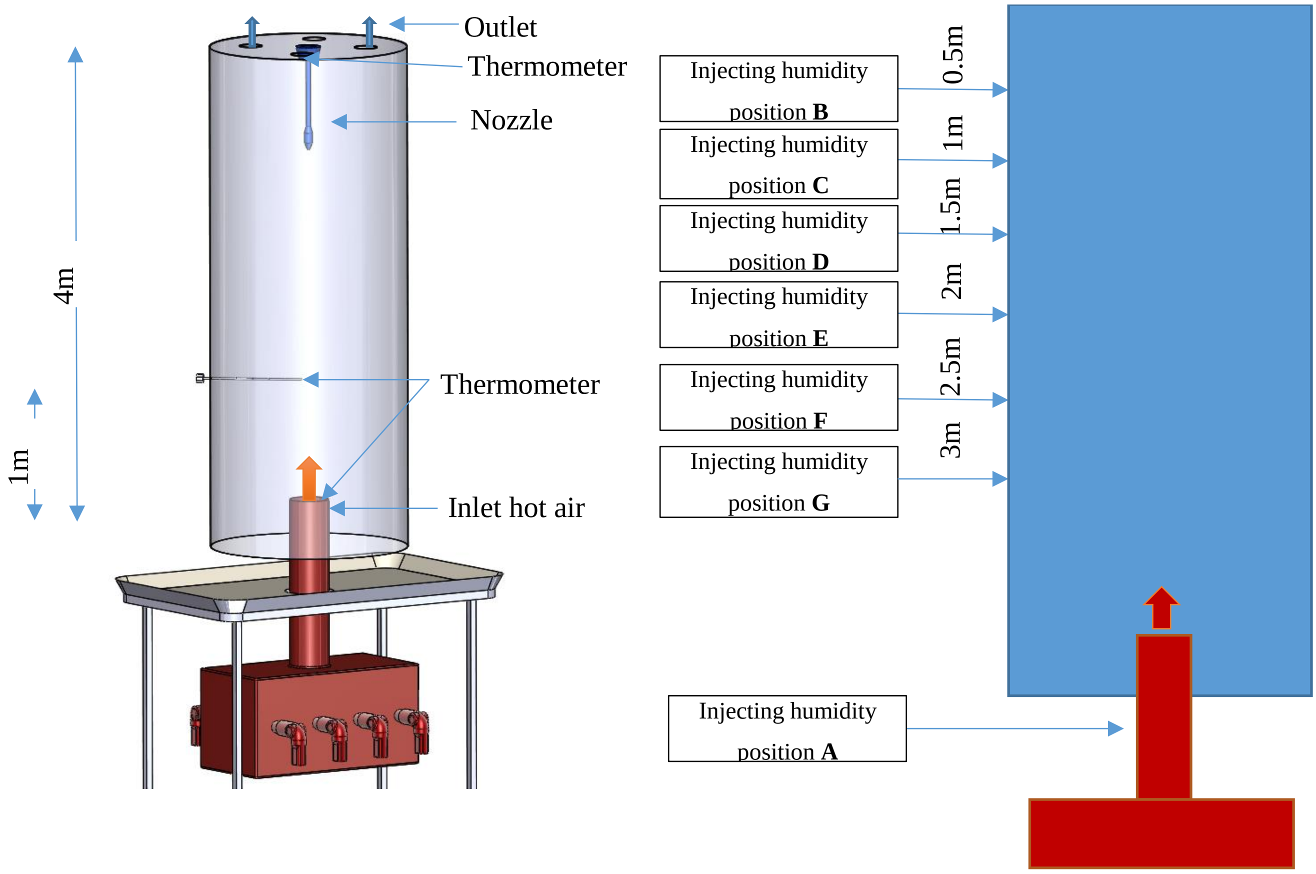

Figure 4-1.*(left) schematic of the spray drying tower; (right)position of humidity injection and sample collection at different heights of spray dryer*

The effect of drying temperature has been investigated on crystallization and contrasting results were reported. Chiou et al (Chiou, Langrish et al. 2008) found the higher the drying temperature the higher degree of crystallization. This finding was subsequently confirmed with further experiment by Islam and Langrish (Islam and Langrish 2010) on high temperature spray drying . The similarity between these experiments was the utilisation of small benchtop spray drying (Islam and Langrish 2010). Contrary to these results, Das et al (Das, Husni et al. 2010) 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(Shakiba, Mansouri et al. 2015, Shakiba, Mansouri et al. 2016) 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 (Wang, Langrish et al. 2010) 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.

Table 4-1. *Lactose with 10% concentration (w/w) Spray dried in various processing conditions*

Run	Humidity Injection	Absolute humidity Inlet/outlet (gr/kg)	Average inlet /outlet temperature range (°C)	Velocity (m/s)	Results(crystallinity, moisture content)
1	No	8/14	105/92	0.31	No crystalline, 3.8%
2	No	21/28	110/95	0.31	Existence of crystalline, 3.5%
3	stage A-25°C	9/25	105/78	0.31	Sticky, 5%
4	stage D-25°C	9/26	105/77	0.31	No crystalline, 4%
5	stage D-100°C	9/30	110/96	0.31	Existence of Crystalline, 3.3%

Apart from the drying temperature, the drying air humidity also has a major role although it has received little attention. Islam et al (Islam, Langrish et al. 2010) 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 (Shakiba, Mansouri et al. 2016) 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.

Materials and equipment

4.1.1 Material

Lactose is a typical powder carrier employed in inhaler and their surface characteristics play a critical role in drug delivery (Pilcer and Amighi 2010). Lactose has relatively high glass transition temperature in comparison with other sugars(Hancock and Zografi 1994). 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 (Mansouri, Woo et al. 2013).

4.1.2 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 4.1). 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(Shakiba, Mansouri et al. 2016) . 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.

4.1.3 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°(Kirk, Dann et al. 2007).

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(Gombas, Szabó-Révész et al. 2002, Lehto, Tenho et al. 2006) . The area under this exothermic peak denotes the required enthalpy for crystallization transition, the larger the area the lower the crystallinity. Sebhatu et al(Sebhatu, Angberg et al. 1994) 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.

Results and discussion

4.1.4 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(Shakiba, Mansouri et al. 2016). It was found the higher degree of crystallinity was achieved at 110°C for lactose in a counter current dryer(Shakiba, Mansouri et al. 2016). 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 4.1 showed that with low ambient humidity (Run1), lactose particle did not crystallize and mainly amorphous particles were generated (according to XRD results Fig 4.2). Run2 was carried out at higher ambient humidity and the XRD result (Fig 4.2-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(Islam, Langrish et al. 2010). According to previous studies, increasing humidity gives rise to better crystallization of the particle(Yazdanpanah and Langrish 2011).

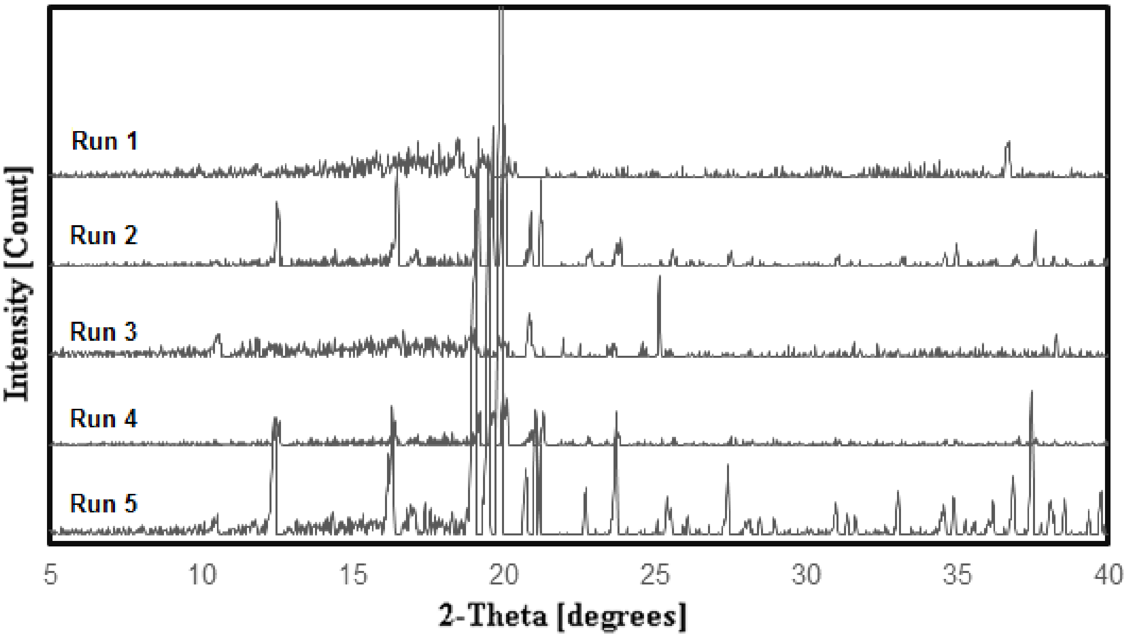

Figure 4-2. *XRD spectrum of lactose in various humidity ratios related to the runs 1-5 in table 1(all other processing parameters are similar).*

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 4.1. This method partially increased the crystallization of lactose particles, Fig 4.2 (Run 3, table 4.1); 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 4.1, 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 4.2 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(Mersmann 2001). 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 (Hancock and Zografi 1994, Islam and Langrish 2010). 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 4.2, for this processing condition, run 5 table 4.1, 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 4.3 compares SEM images of different runs of table 4.1 in which shape of particles partially confirms the XRD results of Fig 4.2. Specifically, existence of crystalline particles in Fig 4.3, run2 and run 5, is evident as there are particles with tomahawk structure in these images.

Table 4-2. *Spray dried lactose 10% concentration (w/w), Average Droplet size 80(µm) humidity injection at different levels (Figure 4.1)*

Run	Absolute Inlet/ outlet humidity gr/kg	Average inlet/outlet temperature range °C	Humidity injection height(m)	Free moisture content (%)	Enthalpy of crystallization(J/g) and degree of crystallinity
1	10/31	110/98	1(C)	3.2	57, 65%
2	11/32	110/97	1.5(D)	2.2	34, 82%
3	10/31	110/97	2(E)	1.7	16, above 90%
4	10/31	110/96	2.5(F)	2.7	48, 75%
5	9/30	110/97	3(G)	4.5	78, 50%

The results of the free moisture measurement, Table 4.1, 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(Makower and Dye 1956). 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.

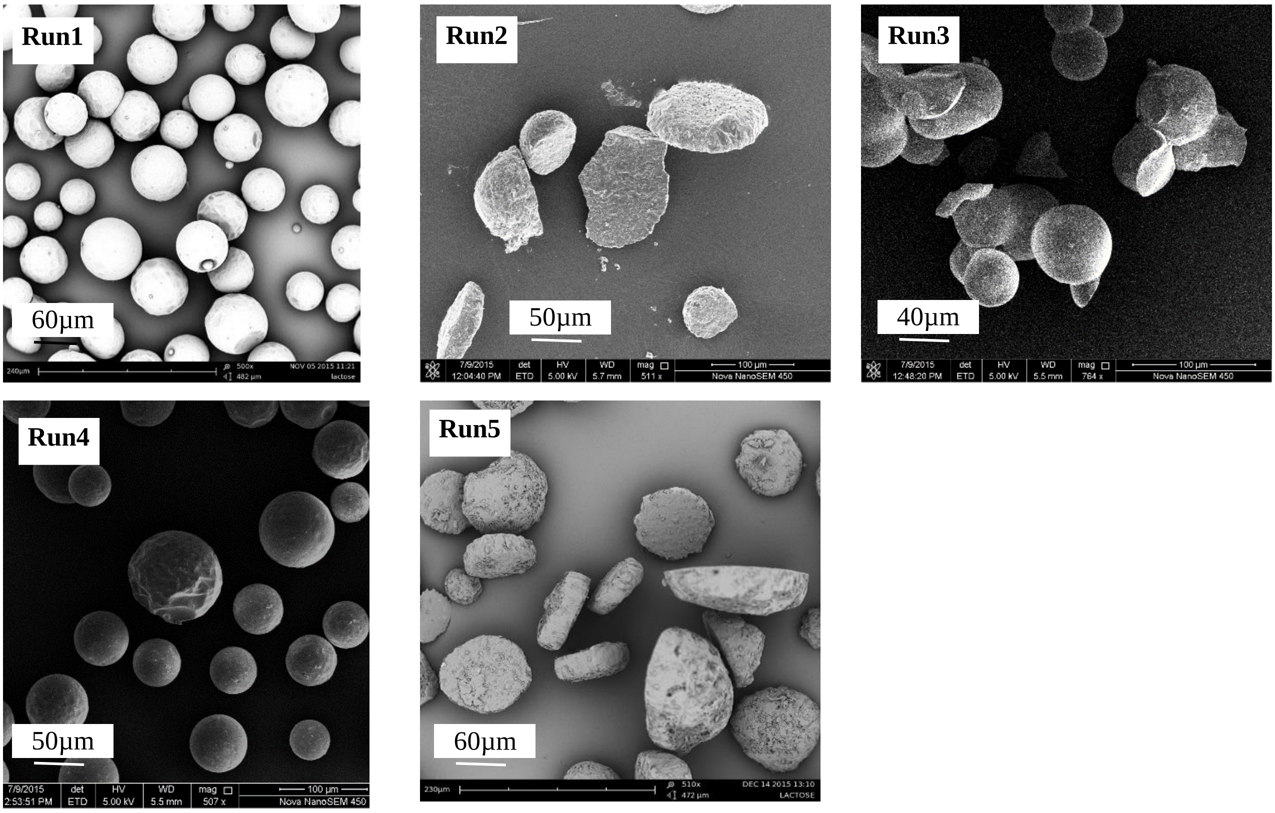

Figure 4-3. SEM result for spray drying in different humidity conditions with regard to table 4.1

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 (Islam, Langrish et al. 2010, Su, Hao et al. 2013). 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(Hancock and Zografi 1994). 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. (Islam, Langrish et al. 2010) 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.

4.1.5 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 4.1. In the next series of experiments, the position of water spray was varied between 1-3 m below the feed atomiser (Fig 4.1). Initially, water spray at the position C (Run 1 table 4.2) resulted in slight increase in degree of crystallinity. XRD test (Fig 4.4) 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 4.2) and similar results were obtained with a higher degree of crystallinity. The shorter peak of recrystallization in the DSC test, Fig 4.5, 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 4.2). It was very interesting that the highest degree of crystallinity was achieved at this elevation of water injection. The XRD results in Fig 4.4 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 4.1, lower degree of crystallinity was achieved (Run 4 table 4.2). According to DSC and XRD results, Figs 4.4 and 4.5, 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 4.2). 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. 4.4 and 4.5, 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 4.2). 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 4.6). 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.

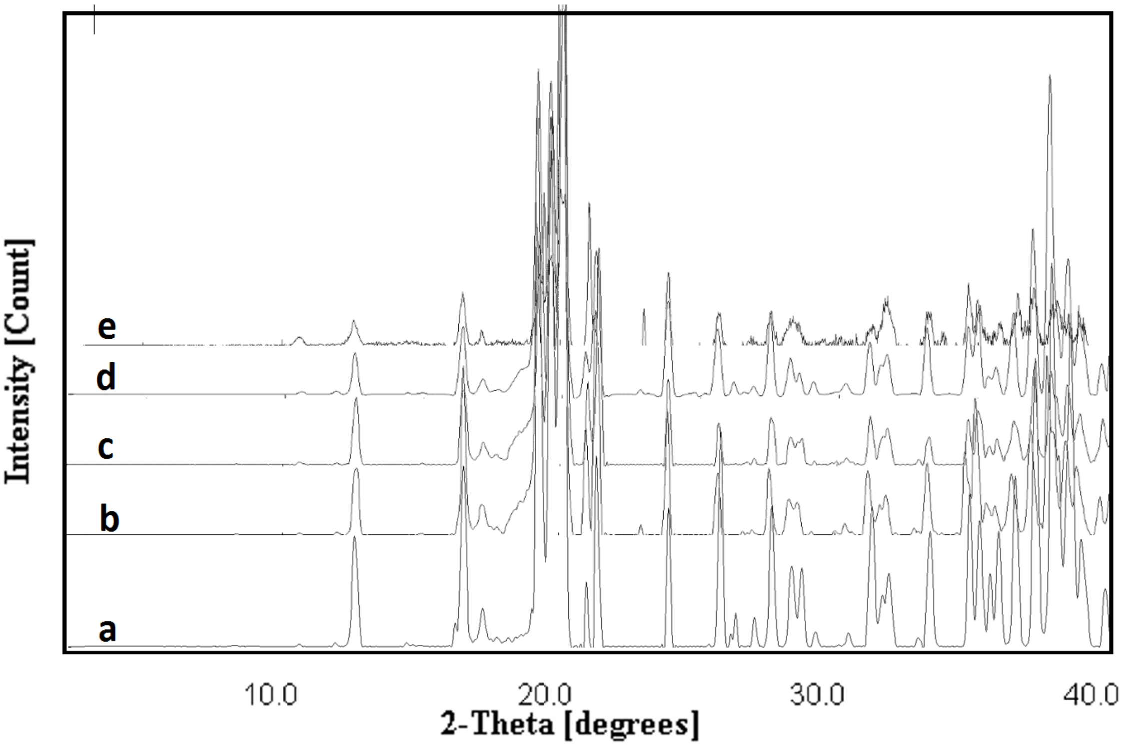

Figure 4-4. *XRD spectrum for spray drying with humidity injection at different stages a) stage E, b)stage D, c)stage F, d)stage C, e) stage G*

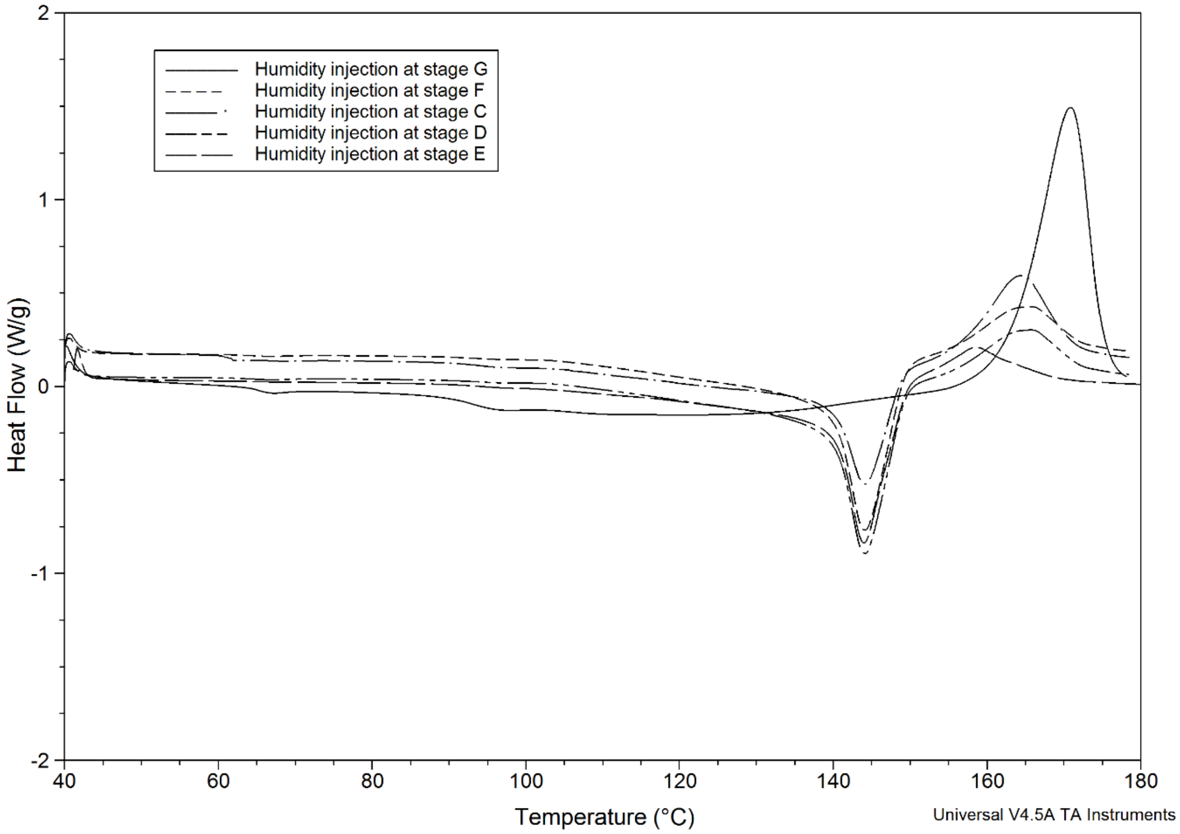

Figure 4-5. *DSC results for spray drying of 10% concentration (w/w) lactose with humidity injection in different height of the tower*

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.

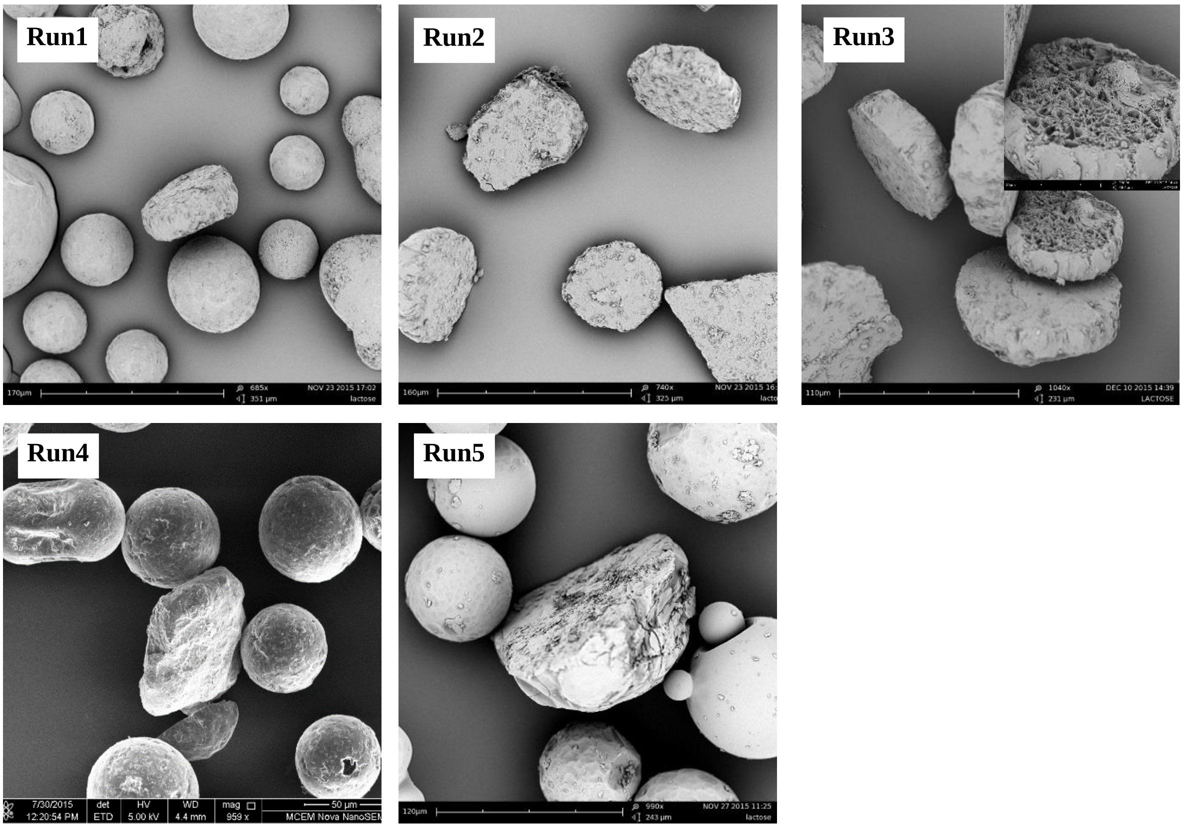

Figure 4-6. *SEM image related to the lactose spray drying with humidity injection concerning processing condition table 4.2*

4.1.6 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 (Langrish and Wang 2009, Islam and Langrish 2010). 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 (Hancock and Zografi 1994).

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 4.3) 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 4.8). 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).

Table 4-3. *Sample collection at different height of the spray dryer, lactose 10% concentration (w/w) and average droplet size 80µm*

Run	Feed temperature	Absolute inlet/outlet humidity gr/kg	Average inlet/outlet temperature range °C	Humidity injection height(m)	Height of formed particle	Height of fully dried particle
1	22	10/17	110/98	No	2	2-2.5
2	100	11/18	110/101	No	1.5	1.5-2
3	22	10/31	110/96	1(C)	2	2.5
4	22	10/31	110/97	1.5(D)	2	2.5
5	22	11/32	110/96	2 (E)	2.5	3
6	22	11/32	110/96	2.5(F)	2	2-2.5

This experiment was repeated, run 2-table 4.3, 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 4.3) 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 4.6. 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 4.3, 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 4.3, 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).

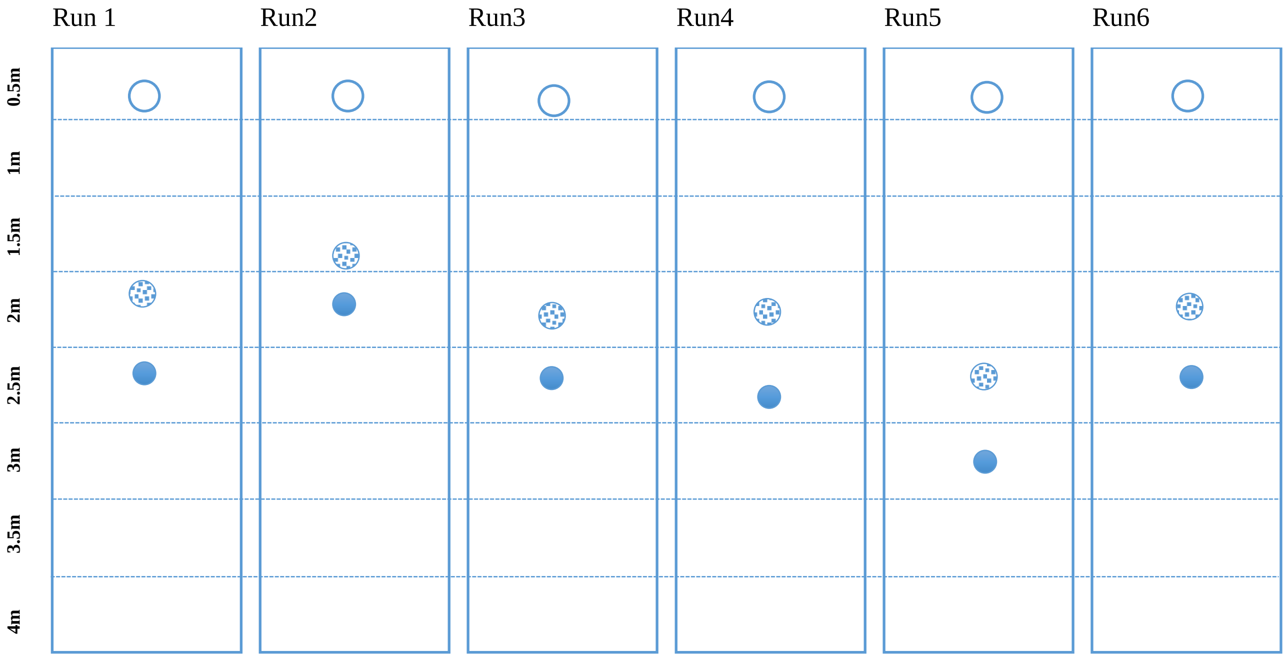

Figure 4-7*.Visualization of collected samples in different heights of the spray dryer based on table 4.3;hollow sphere represents droplet, pattern sphere represents formed particle, solid sphere represents dried particle*

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-table 4.3. 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 4.3 can be visualized in Fig 4.7.

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. (Das, Husni et al. 2010, Das and Langrish 2012) 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. (Woo, Fu et al. 2012) 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). During this period significantly higher degree of crystals was generated, relative to the crystallinity generated once the solidification was completed (Woo, Fu et al. 2012, Parimaladevi and Srinivasan 2014). 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.

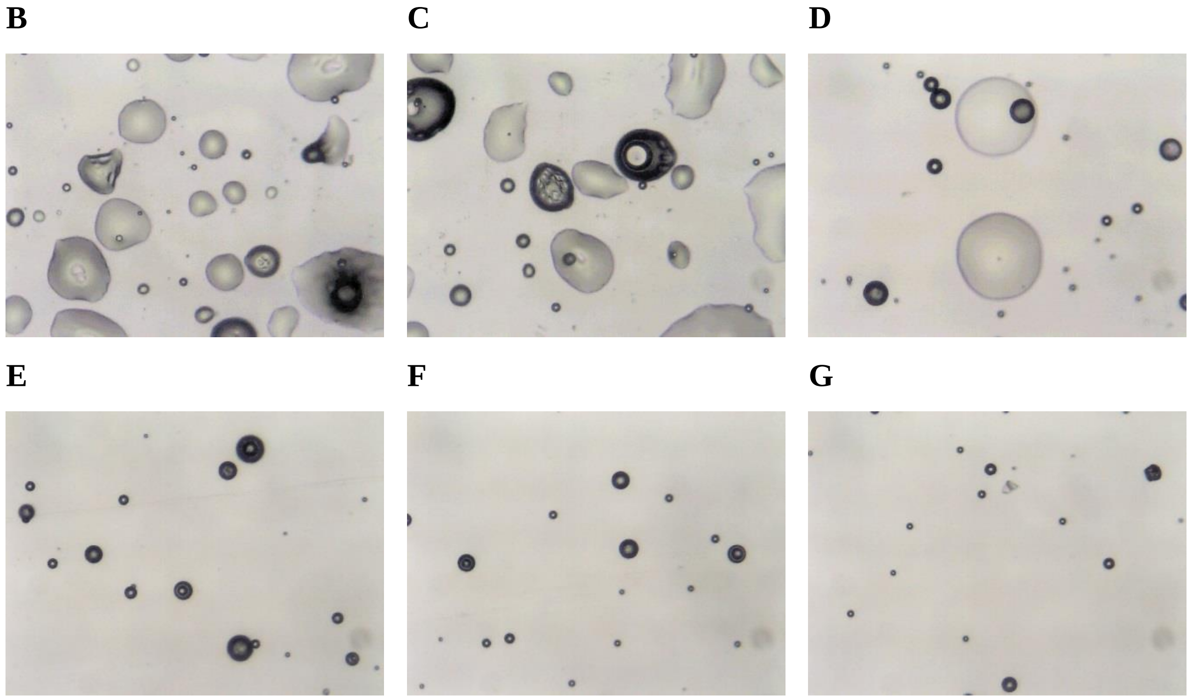

Figure 4-8.*Optical microscopy of collected samples across different height of dryer for drying in 110°C without humidity injection: referred to different stages of spray dryer in Fig 4.3*

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 4.2). The calculated glass transition temperature of particles were within the range of 72– 95°C based on the moisture content of particles in table 4.2. This glass transition temperatures were calculated based on the approach of Hancock and Zografi (Hancock and Zografi 1994) . 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 0.5m 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%.

Table 4-4. *Spray dried lactose 10% concentration (w/w) with humidity injection at different levels*

Run	Average Droplet size(μm)	Absolute inlet/outlet humidity gr/kg	Average inlet/outlet temperature range °C	Feed temperature °C	Free moisture content (%)	Enthalpy of crystallization(J/g) and degree of crystallinity
1	120	10/23	110/90	22	4.5	96, 35%
2	120	11/24	110/92	85	3.7	57, 65%

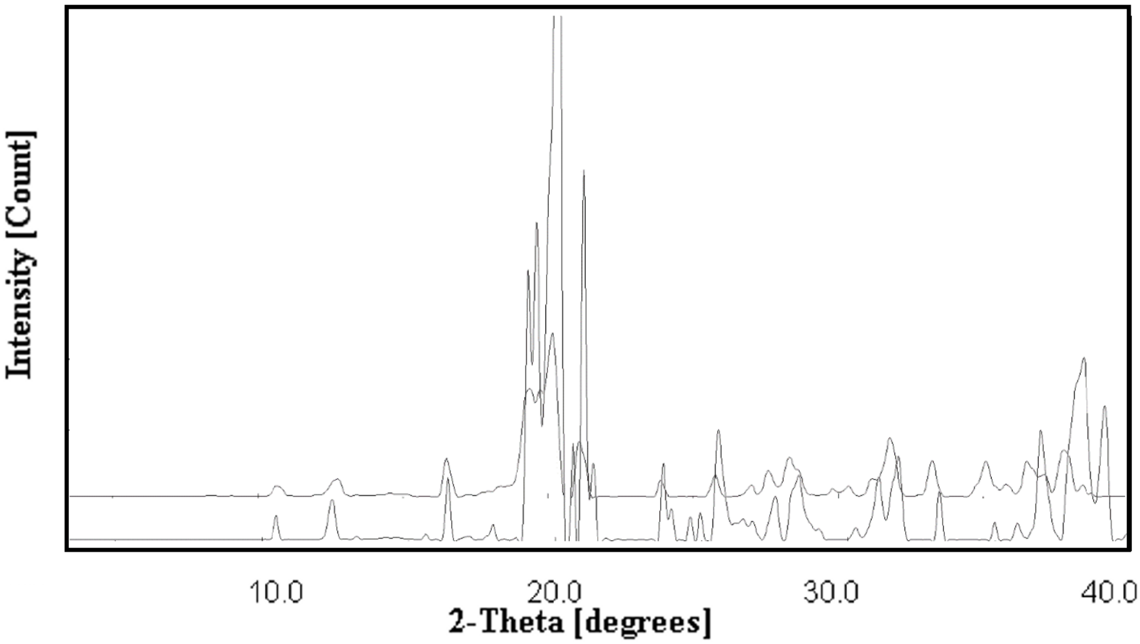

Figure 4-9. *XRD spectrum for particle spray dried with initial droplet size of 120μm with variation in feed temperature*

In the first test, run1–table 4.4, feed in the ambient temperature was atomized. DSC and XRD analysis of this test showed very low degree of crystallinity (Fig 4.9 and Fig 4.10). In the next experiment, run2 table 4.4, 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.

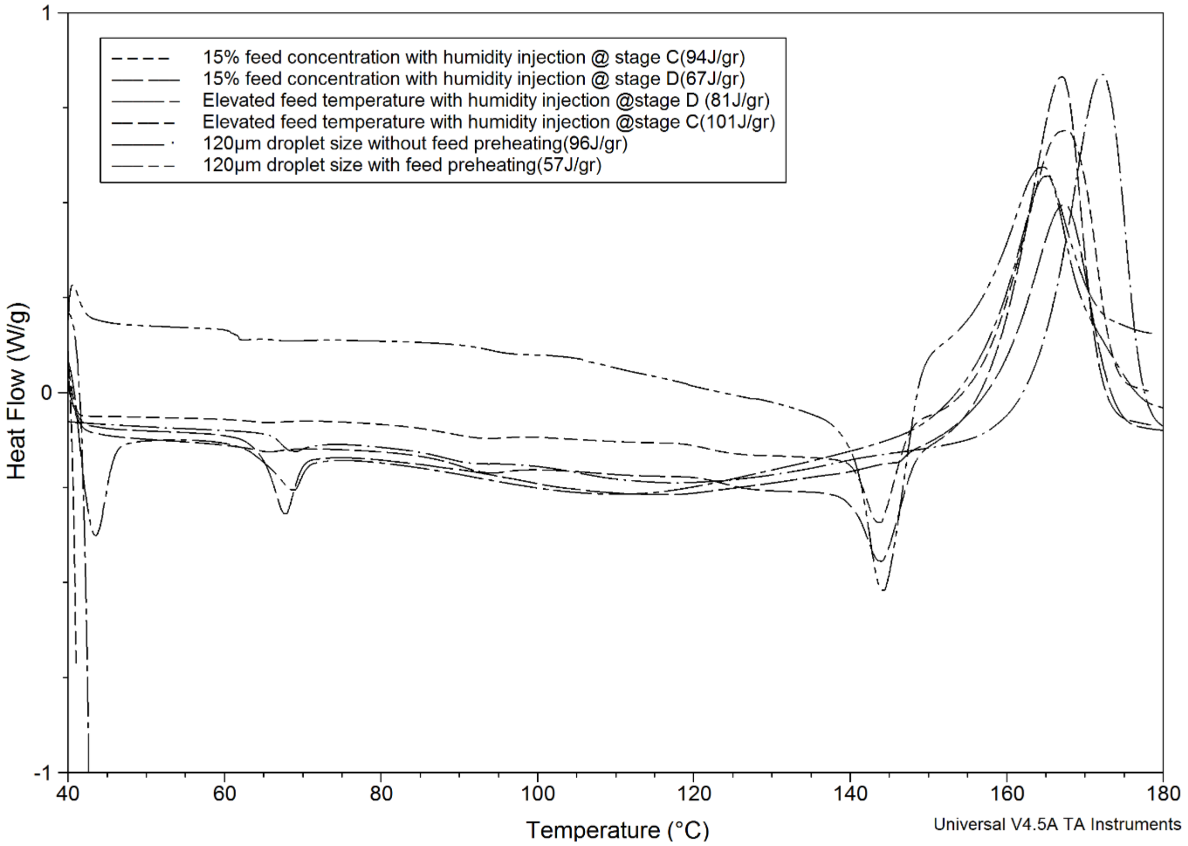

Figure 4-10. *DSC results for different processing conditions (different concentration, feed temperature and droplet size)*

4.1.7 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.

Table 4-5.*Spray dried lactose 15% concentration (w/w) in various processing conditions*

Run	Average Droplet size(μm)	Absolute inlet/outlet humidity gr/kg	Average inlet/outlet temperature range °C	Humidity injection height(m)	Height of fully dried particle	Results, enthalpy of crystallization, moisture content
1	80	8/15	110/98	Non	2	Amorphous, 3.1%
2	80	8/29	110/97	2	2	Very low degree of crystallinity, 3.5% agglomerated
3	80	9/30	110/97	1.5	2-2.5	Crystalline, 67(J/gr), 3%
4	80	9/30	110/97	1	2	low degree of crystallinity,94(J/gr), 3.5%

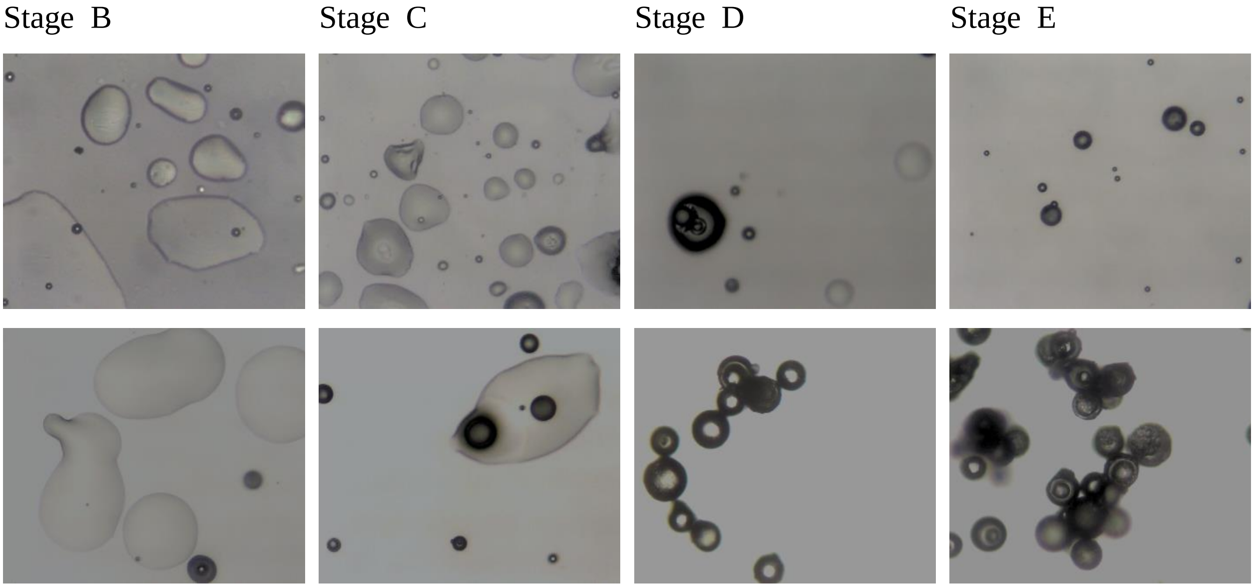

Figure 4-11. *Samples collected from different height of spray dryer, First row) lactose 15% without humidity elevation, second row) lactose 15% with humidity elevation.*

4.1.7.1 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) (Feng, Boraey et al. 2011), 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 at25°C is about 22gr/l. Unexpectedly, the particles were relatively lower in crystallinity when compared to the 10% concentration lactose feed runs (Run 1 – Table 4.5). Particles were collected at different stages of the tower and it showed particle formation occurred nearly one stage earlier than the 10% concentration runs, Fig 4-11. 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 4.5). 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, (Run 3 table 4.5). The SEM results revealed existence of crystalline lactose and XRD (Fig 4.12) 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 4.12, 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.

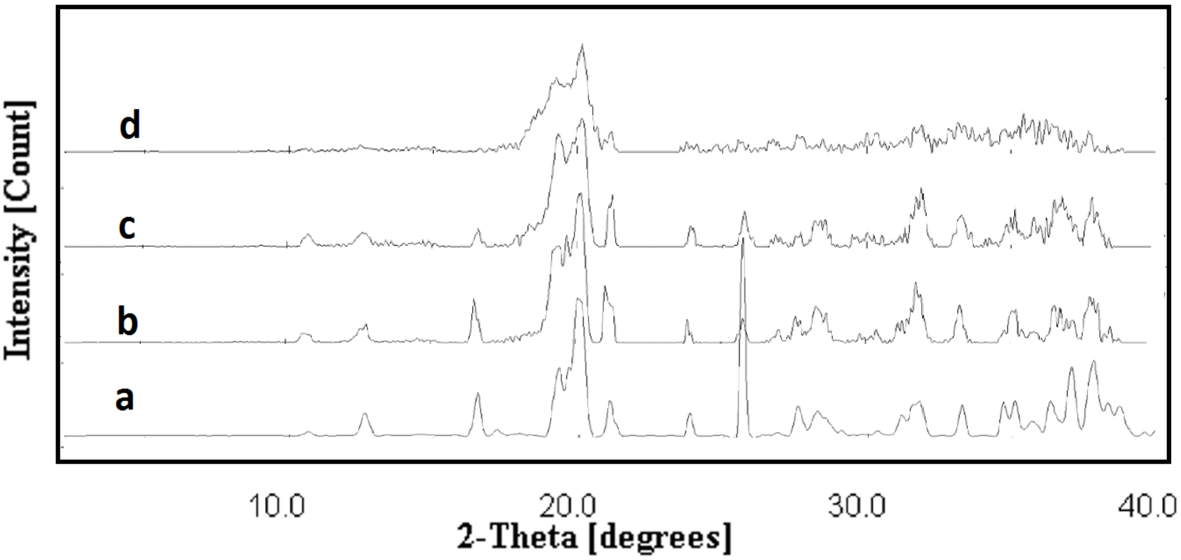

Figure 4-12. *XRD spectrum for spray dried lactose particles of 15% w/w with a)humidity elevation at stage D, b)humidity elevation at stage C, c) humidity elevation at stage E, d) without humidity elevation*

4.1.7.2 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 (Mersmann 2001, Myerson 2002). A higher temperature would amplify the creation of nuclei and the growth process (Mersmann 2001). 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 4.6) 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 4.13, 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 4.13.

Table 4-6.*Spray dried lactose 10% concentration (w/w) in various processing conditions with average droplet size of 80 µm*

Run	Absolute inlet/outlet humidity gr/kg	Average inlet/outlet temperature range °C	Humidity injection height(m)	Feed Temperature °C	Height of fully dried particle (m)	Results, enthalpy of crystallization, moisture content
1	9	110/103	Non	110@6bar	1-1.5	Amorphous, high yield, 3%
2	9/30	110/104	1	110@6bar	1-1.5	Amorphous, low yield, 3.3%
3	9/30	110/104	1.5	110@6bar	1-1.5	Amorphous, low yield 3.4%
4	9/31	110/103	0.5	110@6bar	1-1.5	Amorphous, highly agglomerated, high yield, 3.2
5	9/30	110/98	No	80	1.5-2	Amorphous, 4%
6	9/30	110/98	1	80	1.5-2	Existence of crystalline 101 (J/gr), 3.7%
7	9/31	110/97	1.5	80	2	Existence of crystalline, 81(J/gr), 3.2%

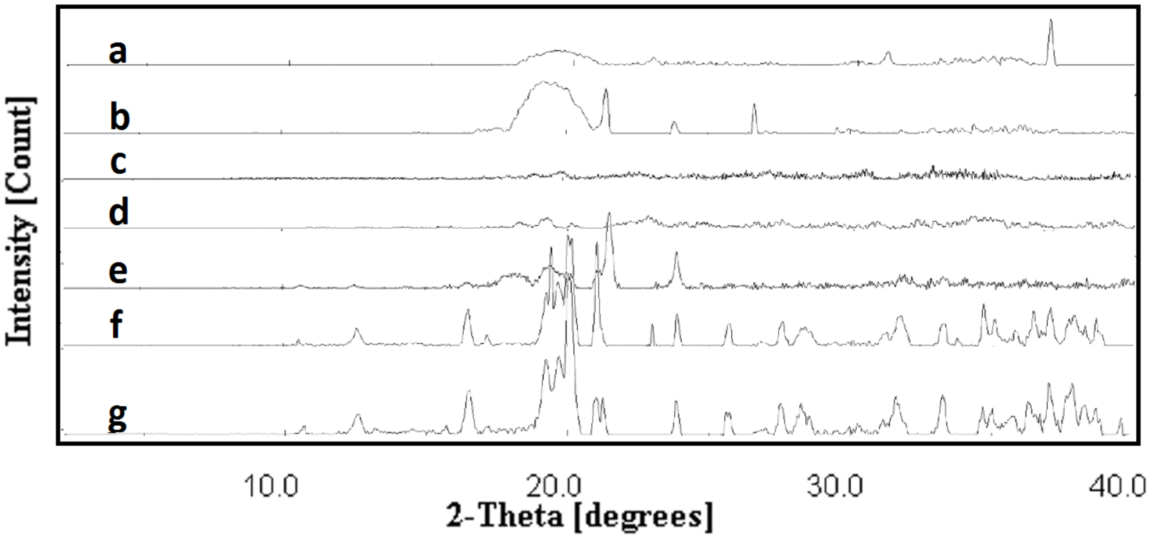

Figure 4-13.*XRD spectrum for spray dried lactose with elevated temperature a) to g) are related to the run 1 to 7 in table 4.6*

In light of these observations, the feed temperature was then reduced to 80°C (Run 5 table 4.6) 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 4.6), showed there is negligible effect on the degree of crystallization compared to the Runs without feed temperature elevation (Fig 4.13). The moisture content of that run was also above 3.5%. In the next experiment (Run7, table 4.6) 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.

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.

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Link to Next Chapter

Although a deeper understanding on the in-situ crystallization process was now obtained from the preceding chapters, the design of any experiments or commercial trials to better understand the in-situ crystallization process is time consuming and is not economical. Furthermore, as illustrated by the preceding chapters, the factors controlling the in-situ crystallization process has complex non-linear interactions. Therefore, there is a strong need for a theoretical predictive approach to guide future experimentalists. The following chapter describes the development of such a predictive approach which incorporates the description of the crystallization behaviour of the spray dried material into the predictive framework.

Chapter five

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5 Zero Order Model for Analysis of in-situ Crystal Formation in Droplet Undergoing Rapid Dehydration[3]

Abstract

The surface structure of the crystalline particles affects the functionality of the particles in drug delivery. Prediction of the final structure of particles that crystallize easily within the spray dryer is of interests of many applications. A theoretical framework was developed for the prediction of crystal structure precipitating on the surface of the particle. Mannitol was produced under different processing conditions in order to validate the theoretical model. The theoretical framework was developed based on the dimensionless Damkohler number (Da), to be an indicator of final particle morphology. Timescales of evaporation and reaction were required for calculation of the Damkohler number. The modified evaporation time scale was estimated based on the time that is available for the crystal to precipitate after supersaturation. The reaction time scale was estimated based on the time scale for induction time. Results showed for the high Damkohler number, $Da \approx > 1$, the surface structure of the particle is rough, while the minor Damkohler showed relatively smooth surface. Additionally, though the beta polymorph was dominant in all of the experiments, alpha polymorph was precipitated in the

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[3] Dimensional analysis of in-situ crystal formation in droplet undergoing rapid dehydration
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experiments with a large Damkohler number. Therefore, this model could be a useful tool for prediction of final structure and polymorph.

Keyword: Crystallisation, Excipient, Polymorphism, Dimensional analysis, Spray-drying

Introduction

Efficiency of drug delivery in form of powder, e.g Dry Powder inhaler, tightly pertains to the characteristics of the excipients. Functionality, morphology and stability of the excipient particles are the key factors affecting the efficiency of this type of drug delivery (Timsina, Martin et al. 1994, Son, Longest et al. 2013, Chen, Ding et al. 2018, Shetty, Park et al. 2018). Therefore, designing engineering particles to tailor particle characteristic to the required application is the way to improve the efficiency (Geng, Dalhaimer et al. 2007, Chen, Ding et al. 2018). Spray drying as one of the well-established technologies in powder manufacturing offers a reasonably good versatility in manufacturing engineered particles (Platz, Patton et al. 2003, Shetty, Park et al. 2018).

Spray drying is widely used in the pharmaceutical industry as a one-step process to dehydrate and micronize products into the particulate form. Formation of amorphous particles is typical during the evaporation process due to the short timescale of evaporation, which does not facilitate organized molecular rearrangement of the spray-dried material. Such particle formation behaviour is mainly observed in materials that are slow to crystallize such as lactose, sucrose or certain proteins e.g Whey protein (Islam and Langrish 2010, Islam, Langrish et al. 2010, Das and Langrish 2012, Shakiba, Mansouri et al. 2016, Woo, Lee et al. 2016).

When the material being spray dried has a fast kinetic of crystallization (FKC), exhibiting crystallization rate, combination of nucleation and growth, in the order (or smaller) of the evaporation time scale, crystalline particles may be formed. Such crystalline particle formation behaviour can be observed in the spray drying of mannitol, (Littringer, Mescher et al. 2012, Littringer, Paus et al. 2013). Controlling the crystallinity of such particles will have a significant impact on the behaviour of the particles. Crystalline particles with different rugosities have been shown to display low surface energetics giving better flowability (Nokhodchi, Maghsoodi et al. 2007). Particles with high crystallinity will also exhibit better stability (Costantino, Andya et al. 1998, Woo, Lee et al. 2016). In certain applications, where mannitol is used as excipients for protein-based active ingredients, there is a need to control and prevent crystallization to preserve the functionality of the active ingredients (Chen, Okuda et al. 2016).

The key to manipulating the crystallization of FKC materials within the spray drying process is to find a delicate balance between the nucleation and growth process within the short time frame. Too rapid evaporation will lead to the insufficient time duration for the crystals to grow leading to the formation of smaller crystallites in the particle; at the extreme, amorphous particle will be formed. At the other end of the spectrum, relatively milder evaporation rates will allow more time for crystal growth leading to the formation of larger crystallites in the particle (Woo, Lee et al. 2016). Controlling this delicate balance is not trivial, as the drying history of the droplets or particles within the spray dryer is not known prior. This control is further complicated when scaling up product formulations from small laboratory spray dryers to production capacity spray dryers, which may exhibit significantly different evaporation rates and drying time scale (Das and Langrish 2012, Littringer, Paus et al. 2013).

There are mathematical approaches available in the literature to help achieve and control this delicate balance for more efficient crystalline particle engineering. Computational fluid dynamics (CFD) modelling can be used to provide detailed information on the drying history (the pattern of heat and mass transfer experienced by the droplet throughout the drying chamber) within the spray dryer (Jayanthi, Zhang et al. 1993, Seydel, Blömer et al. 2006, Mezhericher, Levy et al. 2010). Coupled with detailed droplet drying models [14,15], there is a possibility to predict particle formation and in-situ crystallization within the spray drying chamber. However, it is noteworthy that there is yet to be any work reporting the application of CFD indirectly predicting the in-situ crystallization process in spray dryers. Nevertheless, even if such models are developed in the future, complexity in the CFD technique may not be suitable as a routine tool to guide crystalline particle engineering trials or experiments.

Another mathematical approach, which is less complex and easier to implement, is a dimensional analysis that provides an indicative prediction of in-situ particle crystallization within the spray-drying chamber. The dimensional analysis typically captures the operating conditions of the spray dryer without the need for detailed prediction of the processes within the drying chamber, treating the chamber like a ‘zero dimension black box’. Vehring et al (Vehring, Foss et al. 2007) was first to modify the concept of the dimensionless Peclet number as a parameter to delineate the formation of different morphologies of non- crystallizing particles in spray drying. The mathematical form of this modified dimensionless number is given below,

$$Pe = \frac{k}{8D} \tag{1}$$

Where the denominator and nominators could be denoted as the timescale for the diffusion of solutes within the droplet and the time scale for evaporation (mass transfer coefficient) respectively. The mass transfer coefficient calculated below using the operating conditions of the spray dryer,

$$k = \frac{8\,D\,\rho_g}{\rho_l} \ln\left(\frac{1-Y_\infty}{1-Y_S}\right) \tag{2}$$

D: diffusion coefficient, ρ_g: gas density, ρ_l: liquid droplet density, Y_∞:mass fraction of solvent vapor at the gas phase, Y_S: mass fraction of solvent vapour at the droplet surface.

This approach in essence provides a non-dimensional indication of droplet surface solute enrichment during droplet evaporation, to delineate the formation of different forms of particle crust (Vehring, Foss et al. 2007, Vehring 2008). Modifying this approach, Feng *et al (Feng, Boraey et al. 2011)* used this to calculate an indicative timescale in which the spray dried droplet will reach supersaturation which is taken as a pre-requisite for crystallization,

$$t_{sat} = t_D \left(1 - \left(\frac{C_i E_i}{C_i^*}\right)^{2/3}\right) \tag{3}$$

t_{sat}: required time for the particle to reach saturation at the particle surface, t_D: required time for the particle to be completely dehydrated. C_i: initial concentration, C_i^*: Solubility.

The total drying time available for evaporation was further estimated by dividing the droplet water mass with the evaporation computed by Equation (2),

$$t_D = \frac{d_i^2}{k} \tag{4}$$

d_i: droplet initial diameter,

Taking the supersaturation point as the start of crystallization, the time scale available for crystal growth can then be computed by finding the difference between the time scale computed by Equations (3) and (4),

$$t_{Cry} = t_D - t_{sat} \tag{5}$$

The time scale calculated by Equation (5) is illustrated in Figure 5.1 and was used as an indicative parameter to control in-situ crystallization in spray drying. This approach was further compared with experimental data from a small-scale Buchi spray dryer and was shown to be effective in predicting the degree of crystallinity of spray-dried leucine particles (Feng, Boraey et al. 2011). Examining this crystallization prediction framework, Equation (1)-(5), the crystallization characteristics of the spray-dried material is not accounted for. In fact, the only material property accounted in this framework is the solute binary diffusivity in water and the solubility of the solute. While this approach may indicate the timescale available for crystal growth, it does not capture the kinetics or the rate of crystal growth specific to the material spray dried. Therefore, the capability of this approach to capture the experiments trends reported may be fortuitous. In addition, this framework also does not provide a predictive indication of the size of the crystallites produced by the drying process. It is well reported in the literature that different drying histories will produce various crystallites sizes, which will subsequently affect the overall morphology of the particles.

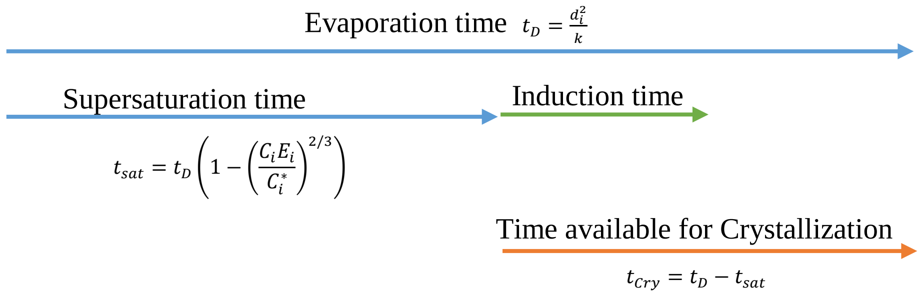


Figure 5-1. *Illustration on the predictive framework of Feng et al. (Feng, Boraey et al. 2011) comparing with the framework proposed in this communication (blue is the method of Vehring et al (Vehring, Foss et al. 2007), orange is the method of Feng et al. [16], green is the method proposed in this work)*

This communication reports the development and validation of a spray drying non-dimensional crystallization predictive framework, which accounts the crystallization characteristics of the spray-dried material. As a starting point, the framework was built upon and expanded the basic framework by Vehring and co-workers (Vehring, Foss et al. 2007)reported in the literature. The theoretical framework was developed for fast-to-crystal materials, adopting mannitol as a model material. Validation experiments were further undertaken by counter current spray-drying of mannitol.

Theoretical development

One of the key interpretation in the framework proposed by Feng *et al.* (Feng, Boraey et al. 2011) is that the entire time duration beyond surface enrichment saturation point is available for crystal growth, Fig 5.1 (surface enrichment saturation point is the point that the surface of the particle reaches saturation due to continuous evaporation). Longer time duration will give more time for crystallization and vice-versa. In the actual crystallization process, there will be two distinct crystallization periods. The initial duration will be an induction period, which is in essence a combination of nucleation and growth, until detectable crystallites are formed. This will then lead to the growth-dominated period in which the bulk of the crystallinity is generated (Mersmann 2001). Therefore, capturing the induction period, which is the premise of this communication, is important because it will give an indication of the time duration available for crystal growth (Fig 5.1).

Following the approach by Kashchiev *et al.* (Kashchiev, Verdoes et al. 1991), the following semi-empirical expression can be used to calculate the induction time of mannitol,

$$t_{ind} = \frac{1}{JV} + \left(\frac{\varepsilon}{a_n J G^{n-1}}\right)^{1/n} \tag{6}$$

Where J is the nucleation rate (m^3 /s), V is the volume of the droplet (m^3), ε is the ratio of the volume of the detectable size of nuclei over the droplet volume, a_n is the shape factor of the precipitated crystals (m^2) and G is the growth rate during the induction period (m^2/s). This equation can account for one-, two- and three-dimensional growth behaviour within the induction period, denoted by the dimensionless ‘n’ parameter. In view that mannitol typically grows to become needle shape-like, it can be approximated as one-dimensional growth (Shoji and Takiyama 2012) denoted by a ‘n’ of two (two-dimensional growth will have a value of three etc.). In addition, the shape factor $, a_n,$for one-dimensional growth is equal to the cross section of the precipitated crystal.

$$t_{ind} = \frac{1}{JV} + \left(\frac{\varepsilon}{A_c J G}\right)^{1/2} \tag{7}$$

The nucleation rate was computed using the classical empirical correlation considering homogenous nucleation (Mersmann 2001),

$$J = A \times exp\left[-\frac{16\pi\gamma^3 v^2}{3K^3T^3(\ln S)^2}\right] \tag{8}$$

Where A is a constant usually taken 10^{30} and γ accounts for interfacial energy that was adopted from experimental study for higher precision (Su, Hao et al. 2013).

The growth rate of mannitol was calculated using the following expression available in the literature (Shoji 2012) ,

$$G = K_G e^{-(\frac{\Delta E_g}{RT})} \times \left\{1 - e^{(-c_g[L+\beta])}\right\} \sigma^g \tag{9}$$

Where G: growth rate (m/s), Kg: linear growth constant(m/s), ΔE_g: activation energy (Jol/mol) ,c_g: constant in growth rate expression (1/m) β: constant in growth rate(m), L: crystal size (m), σ:relative saturation ($\frac{C^*}{C} - 1$), C^*= saturation concentration (kg/Kg), C: concentration (kg/Kg), g: growth rate order.

The shape factor a_n in Equation (6) requires the characteristic dimension of the crystal precipitated during the induction period. Droplet sizes typically encountered in spray drying ranges from tens to hundreds of microns. Typical dimension reported in the literature measured from relatively larger scale batch cooling crystallization experiments are in the order of tens of microns, hence, may not be directly applicable to in-situ crystallization within sprayed droplets. One would expect the initial size of the crystals produced in sprayed droplet during the induction period to be in the sub-micron length scale. In the absence of reported experimental data for sprayed droplet crystallization, this characteristic length scale was estimated with the critical nucleus radius given by the following expression below.

$$r^* = \frac{f_S \gamma v}{3 f_V K T ln\, S} \tag{10}$$

Where f_s and f_V are area and volume shape factor for crystal determined empirically for mannitol, S: saturation ratio (C^*/C).

The critical nucleus radius represents the minimum possible nucleus size from which growth can occur. Any nucleus smaller than this size may be dissolved in the mother liquor without proceeding to further growth. The characteristic length scale of the crystal precipitated during the induction time was arbitrarily assumed as one magnitude larger than the critical nucleus radius.

The ratio of the volume of the detectable size of nuclei over the droplet volume, α, is a material-specific parameter conventionally back-calculated from batch cooling experimental crystallization data using Equation (6). There is, however, yet to be any value reported for mannitol crystals. For this communication, the cooling crystallization data of Su et al. (Su, Hao et al. 2013) was then used from which the α for mannitol was determined to be $2.5\text{x}10^{-3}$. For brevity, details of the back-calculation undertaken is included in the Appendix.

Taking the estimated time available for crystallization (Equation 5) and normalizing by the induction time (Equation 6), the following ratio is obtained.

$$Da = \frac{t_{cry}}{t_{ind}} \qquad (11)$$

This ratio provides an indication of the proportion of the droplet drying time available for crystal growth of the material, which actually contributes to crystal size, relative to the induction period which is dominated by the generation of the number of crystal nucleus. In essence, if we view the crystallization process as a kind of ‘reaction’, Equation (11) is analogous to the Damkohler number which is a non-dimensional parameter indicating the time scale of reaction to the overall timescale of a process (Fogler 1999). Concept of Damkohler number relates mass transfer to chemical reaction and explain different physical aspect of a reaction according to ratio of these two rates. In the current work, this will be referred to as the “modified Damkohler number” developed for a micron scale droplet crystallization process.

Experimental method

The modified Damkohler number was evaluated with experimental data generated with spray drying of mannitol using a counter-current spray tower available in Monash University. The details of experimental apparatus were reported in the previous work(Woo, Lee et al. 2016) .

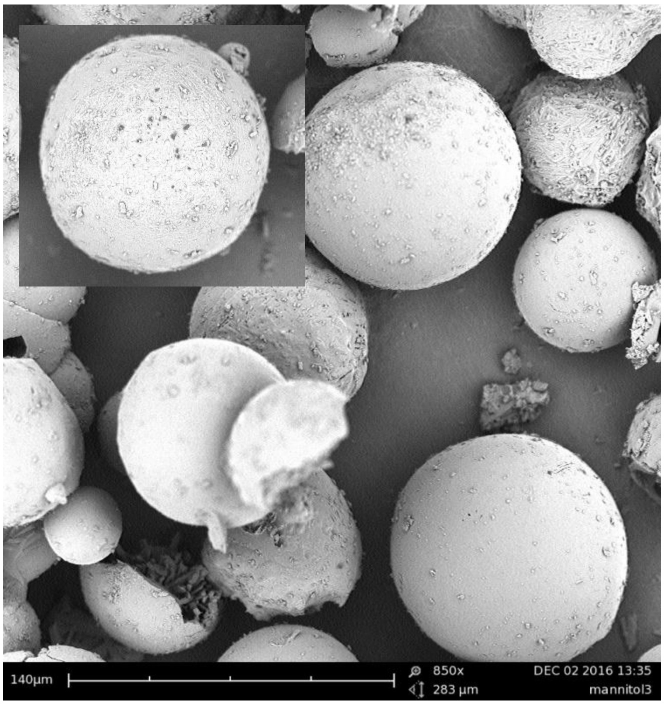
Table 5-1.*Experimental matrix for the spray drying of mannitol*

	Average Drop size, µm	Initial feed concentration, %wt	Inlet temperature, °C	Outlet temperature, °C	Drying air flow rate(m^3/min)
1	50	10	94	69	1.35
2	80	10	90	66	1.35
3	80	10	85	63	1.35
4	80	15	105	75	1.50
5	120	10	100	72	1.50
6	120	10	86	62	1.35

5.1.1 Analytical tests

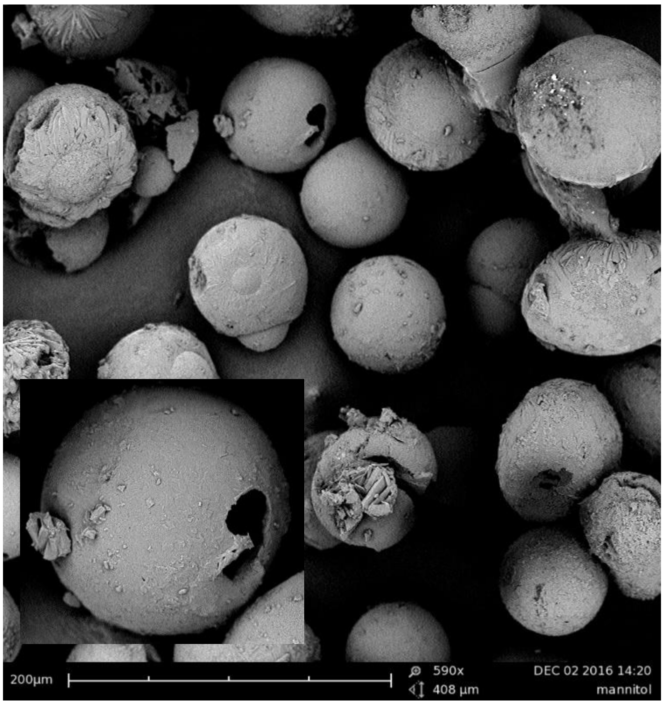
Scanning electron microscopy is a quick method for observation of surface particle characteristics. In this study a FEI Nova Nano SEM 450, a Phenom benchtop SEM microscope with magnifications of 1 million X, was used for observing precipitation of crystal on the particle surface. Also, XRD method was 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 addition, a series of Absorbance FT-IR test was carried out to complement analysing the crystalline peaks and polymorph detection. An Agilent Cary 630 spectrometer was used to measure the intensity peaks in the range between 650-1500 where the main peaks of absorbance of infrared are detected for D-mannitol polymorphs.

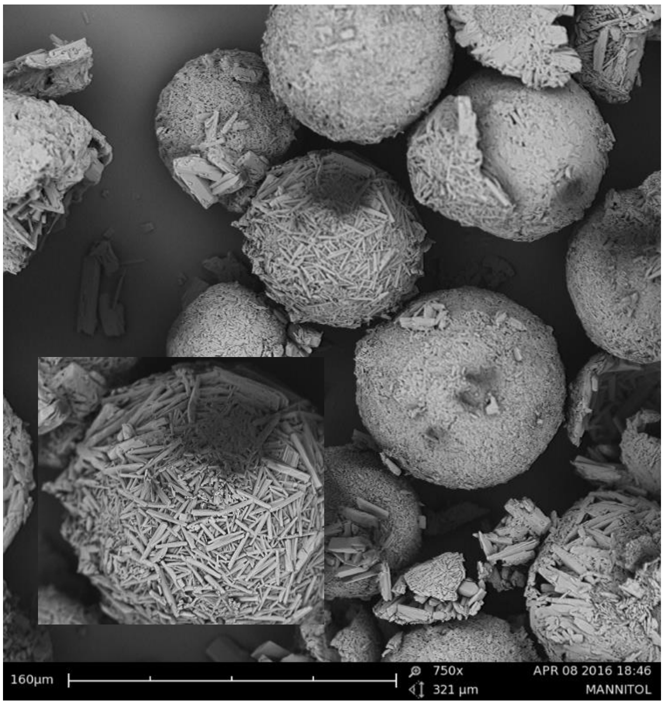


Run 1

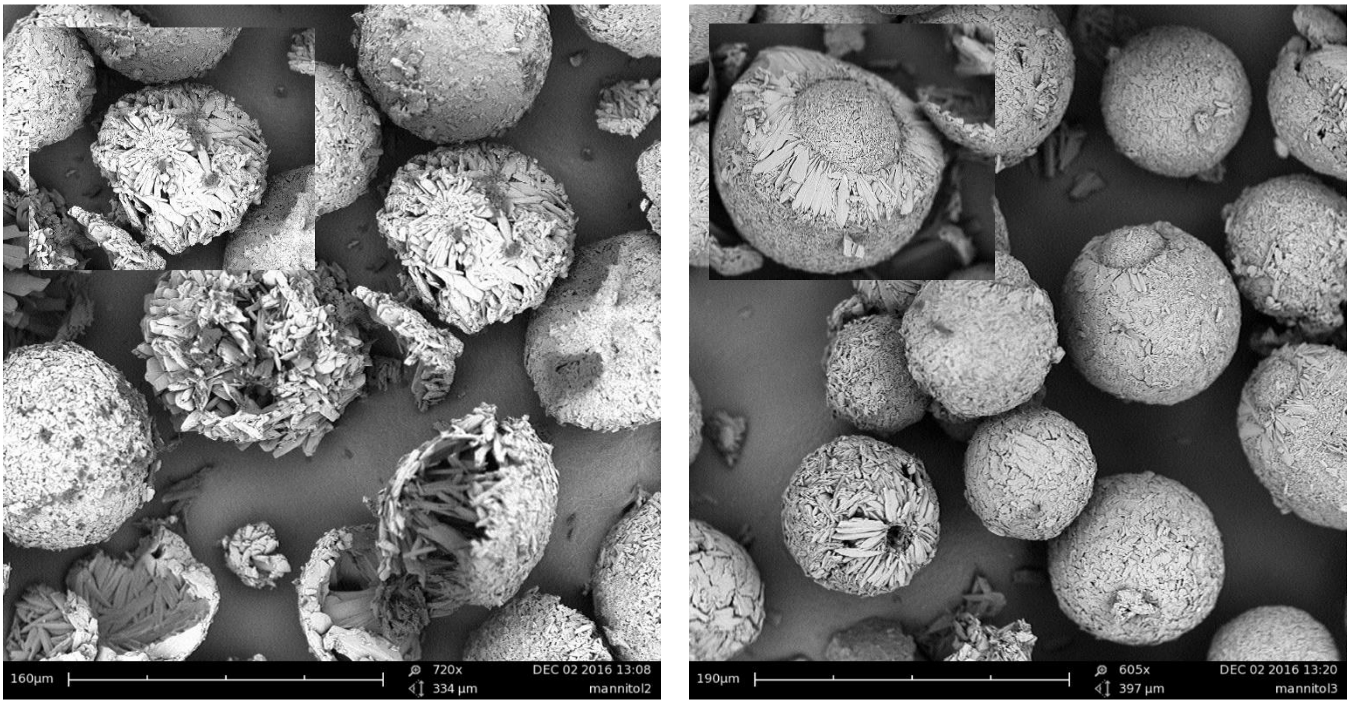
Run 2



Run 3



Run 4



Run 5 Run 6

Figure 5-2.*Scanning electron microscopy of spray dried mannitol according to Table 5.1 conditions*

Results

5.1.2 Morphology of the spray dried particles

In order to assess the mathematical framework proposed, a series of experimental studies were undertaken to produce different possible combinations of induction time and precipitation time. According to the previous research, extending the wet time of the particle influences kinetic of crystallization(Shakiba, Mansouri et al. 2017). Based on extension wet time of the particle, the processing conditions, e.g. droplet size, temperature and drying air flow rate were varied. The different processing conditions used are shown in Table 5.1.

The first sample was prepared with 10% concentration and droplet size of an average of 50µm. The details of processing condition are given in table 5.1. The SEM image, Fig 5.2, shows the surface morphology of the particle generated in Run1 is smooth-like with almost no visible precipitation of large crystal on the surface of the particle. Increasing the droplet size to an average of 80µm in Run 2 resulted in similar observations to Run1. The SEM result for the Run 2, fig 5.2, shows the surface of the particle was smooth. The only main difference relates to the existence of a hole or crack in these particles. It is interesting that cracked particles in Run 2 were almost hollow and there are large elongated crystals formed inside the particles despite the exterior surface of the particles that are smooth. Smooth particle surface is an indication of very fine crystals formed as XRD analysis which will be presented later on indicates that all the experimental runs in this work resulted in the production of crystalline particles.

The drying temperature was reduced in Run 3 to further investigate the possibility of the effect of a slower evaporation rate on the surface morphology of the particles. The SEM images, Fig 5.2, for Run 3 showed particle with relatively smooth morphology with cracks and holes similar to that from Run 2. In view that the temperature change employed did not result in a significant change in the particle surface morphology. This delineates the surface crystallization behaviour, there initial spray solute concentration was increased and at the same time the drying temperature was increased with the aim of producing a higher rate in which supersaturation was achieved during spray drying. SEM analysis for Run 4 (Fig 5.2) revealed that such conditions resulted in particles with a semi-rough surface containing many distinct crystals. There is no hole on the outer surface of the particles and entire surfaces are intact though cracked particles were observed. The latter was probably due to the manual handling of the particles during analysis.

To further investigate the effect of a potentially longer wet time of the particle, in Run 5, the droplet size was increased to the average of 120µm while the other drying conditions almost remained the same as Run 4. SEM analysis showed that the surface of the particles was very rough with the reasonably large elongated crystal formed on the surface of the particle. Further reduction of the drying temperature and the drying airflow in Run 6 resulted in smaller and more elongated crystal grains when compared to that in Run 5. The conditions in Run 6, however, produced interesting sunflower like structure. The sunflower-like structure is composed of relatively large elongated crystallites ordered in a hemispherical pattern on the particles. To the best of the authors' knowledge, such Janus crystalline behaviour has not been reported before for large and small-scale spray drying of mannitol particles. We speculate that this is an artefact of the countercurrent approach to spray drying which will be discussed later on in this work.

5.1.3 FTIR analysis

As expected the spectrum of FTIR (Fig 5.3) shows that all of the particles mainly contain beta-anomer of D-mannitol. The pattern contains all the peaks related to the beta mannitol . Comparing the peaks for Run 1 with FTIR pattern of another polymorph of mannitol shows that the peaks in the range between 1350 and 1450 representing some degrees of another polymorph in addition to beta anomer. The FTIR spectrum of Run 3 shows the same pattern of beta polymorph but the intensity of the peaks was significantly weaker compared to other Runs.

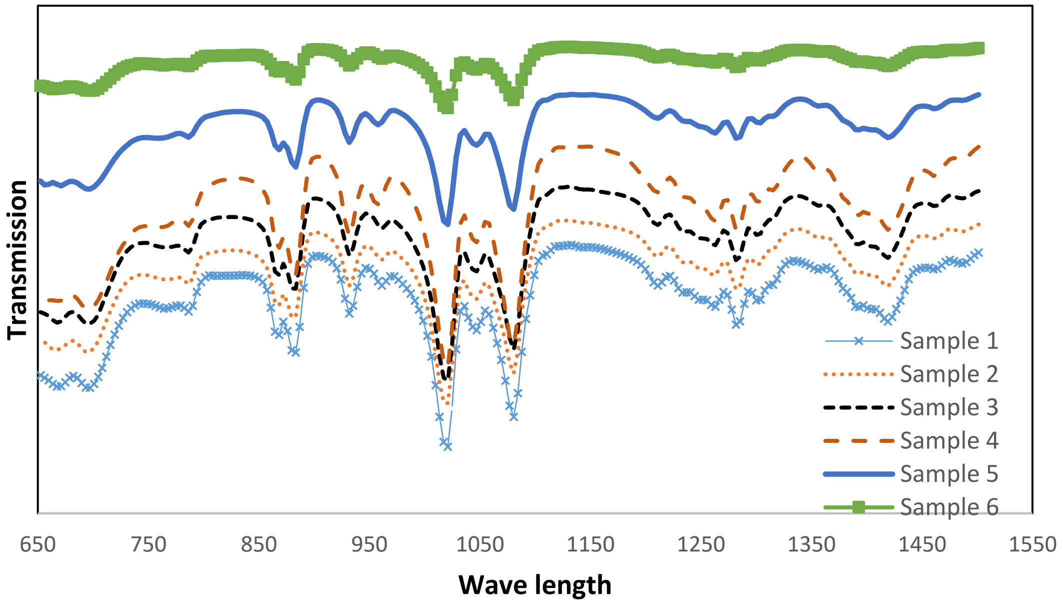


Figure 5-3.*FTIR spectrum of spray dried mannitol according to the condition of Table 5.1.*

5.1.4 XRD analysis

The spectrum of XRD test is shown in fig 5.4. The domination of beta polymorph which was recognized by FTIT test was confirmed by the XRD result. The intensity peaks for the all Runs represent two main peaks of the beta polymorph which appeared in 14.5˚ and 16.5˚ respectively. The XRD spectrums, Fig 5.4, of Run 4 and Run 5, also showed two short peaks around 13.5˚. These peaks are characteristics of alpha anomer of D-mannitol. Therefore, Runs 4 and 5 both contain some degree of alpha mannitol as well.

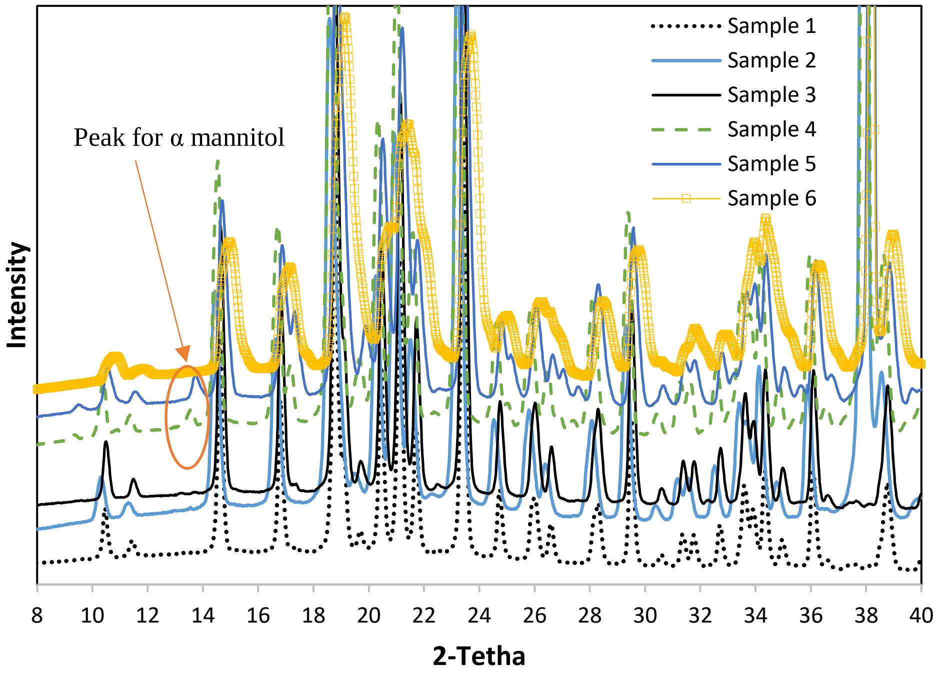


Figure 5-4. *XRD spectrum of spray dried mannitol according to the condition of Table 5.1.*

5.1.5 Implementation of the modified-Damkohler theoretical framework

The premise of the estimation from the framework developed above is that a constant evaporation rate, based on the initial air-droplet conditions, was assumed throughout the droplet drying history. This is a simplifying assumption taking pure water evaporation characteristics as a baseline for comparison and had been previously adopted by Vehring et al.(Vehring, Foss et al. 2007) and Feng *et al.(Feng, Boraey et al. 2011)* ; a simplified indicative prediction in contrast to detailed CFD and one-dimensional modelling reported in the literature (Jayanthi, Zhang et al. 1993, Seydel, Blömer et al. 2006, Mezhericher, Levy et al. 2010). Examining Equation (2), this was estimated mainly by the temperature and humidity of the drying air. In the report by Feng *et al. (Feng, Boraey et al. 2011)*, based on their co-current spray drying configuration, the inlet hot air conditions were adopted. For the counter-current spray-drying configuration used in this communication, the top air-dry bulb temperature and the measured humidity was used for Equation (2) to reflect better the initial drying conditions experienced by the droplets. The wet bulb temperature corresponding to these top outlet air conditions was adopted as the particle temperature for the calculation of the driving force for evaporation (Equation 2) and the surface enrichment process (Equation 3).

For the induction time computation, the temperature of the particle should be estimated. The wet bulb temperature would represent the lowest possible temperature experienced by the droplet during the induction process. As the droplet reaches supersaturation and during the initiation of solid precipitation, there is a possibility that the droplet temperature may increase beyond the wet bulb temperature due to possible evaporation. The upper bound of this possible particle temperature is the outlet dry bulb temperature. Reported experimental results using single droplet drying experiments dehydrating mannitol droplets revealed that the crystallization process might happen at temperatures between the dry bulb and the wet bulb temperatures (Har, Fu et al. 2017). Based on this past report, the upper bound of the droplet temperature in which the crystallization induction may occur was arbitrarily taken as 1/3 the temperature difference between the dry bulb and the wet bulb temperature, above the wet bulb temperature.

Table 5-2. *Calculation of crystallization kinetic and processing timescales*

	Evaporation time	Surface enrichment time	Time available for crystallization	Induction time	Da(1/3 estimation)	Da(wet bulb)
1	0.45	0.25	0.204	0.7	0.29	0.052
2	1.21	0.645	0.56	0.9	0.62	0.12
3	1.29	0.68	0.607	1.47	0.41	0.11
4	1.06	0.488	0.573	0.285	2.01	0.25
5	2.24	1.26	0.95	0.65	1.53	0.31
6	2.91	1.55	1.36	1.4	0.97	0.33

The mass transfer coefficient was calculated using the Ranz-Marshall equation. Droplet-air relative velocity was estimated based on the velocity of the countercurrent drying air. Calculation of the mass transfer coefficient is given in the Appendix. For the different experimental cases undertaken in this communication, the average initial droplet was adopted as the representative droplet diameter. Table 5.A2 collates all the constants and fluid or droplet properties used in the computation of the model.

Discussion

It will be important to first discuss the experimental trend before comparison with the predictive framework proposed. The discussion that follows will examine the experimental trend from the perspectives of the different operating parameters. This is based on practical considerations in operating a spray dryer to control in-situ crystallization within the drying chamber.

Based on varying the drying temperature, the trend showed that for particles generated with similar droplet size (Runs 2, 3, 4 and Runs 5 and 6 another droplet size), higher drying temperature in general led to rougher particle surface delineating the formation of larger crystals on the particle surface. This corresponds with the observations of Mass et al (Maas, Schaldach et al. 2011) but in contrast with the observations of Littringer et al who reported lower drying temperature giving rise to particles with larger crystals for mannitol (Littringer, Paus et al. 2013). It was further argued by Littringer et al. that the different scale of the spray dryer will also lead to different drying history and subsequently different correlations with the drying temperature (Littringer, Mescher et al. 2012). Therefore, such comparison may have limited value because at the core of the discussion, it is the different drying history that leads to various crystallization behavior. In the countercurrent dryer, in the early stage of the drying particles encounter lower temperature and progressively the temperature increases. This would result in supersaturation in lower temperature compared to the co-current dryer. As the droplets travel down the column towards the progressively hotter drying air the droplet will experience a progressive increase in temperature. In contrast, in a co-current spray dryer, the droplets or particles will experience a progressively reducing temperature which may lead to significantly different drying history.

Evaluating crystal surface morphology from the perspective of changes in the initial sprayed droplet , it shows that larger droplets tended to give rise to the rougher surface. Runs 5 and 6 which were generated with an average droplet size of 120µm resulted in rougher surface compared to Run 1 and 2 which were produced with an average droplet size of 50 and 80µm respectively. A larger droplet size in general delineates more time available for evaporation. Such a simplistic interpretation and correlation, however, may be affected by the scale of the spray dryer as highlighted in the literature(Maas, Schaldach et al. 2011, Littringer, Mescher et al. 2012).

Our first attempt analyses the results collating all the factors above into the drying history of the droplets, based on the approach by Vehring et al (Vehring, Foss et al. 2007) outlined in the introduction, was to evaluate the time available for evaporation of the droplet. The calculated timescale for evaporation is given in Table 5.2 and they can be classified into two sets of data. Run 1, 2, 3 and 4 had shorter time available for evaporation (0.45-1.25 s) and displayed smooth and semi-smooth mannitol particle surface morphology, namely amorphous like surface with very fine crystals. In contrast, Run 5 and 6 with relatively longer time available for evaporation (2.24-2.91s) exhibited rougher particle morphology due to the generating of larger crystals. This trend may seem logical as there are reports in the literature to support this observation; high evaporation rates (shorter time available for evaporation) will give rise to very fine crystal resembles amorphous particle and vice versa (Myerson 2002). The discrepancy was, however, observed when comparing within the runs within the two groups. Comparing Run 3 and 4, the latter had a shorter time available for evaporation but exhibited rougher surface morphology due to larger crystals formed. Similarly, comparing Run 5 and 6, the latter had a longer time available for evaporation but exhibited finer crystals. Therefore, while the use of the time available for crystallization analysis may be suitable for comparison between big changes in the drying history of the droplet, it may not be suitable to discern the effect of small changes of the drying history on in-situ crystallization.

Similar comparison and discrepancy were also observed when analysing the results based on the time available for crystallization. This approach was proposed by Feng *et al.* (Feng, Boraey et al. 2011) in which a longer time available for crystallization is expected to produce a higher degree of crystallinity and vice versa. When applying this concept for the prediction of the crystal size, the similar discrepancy between Run 3&4 and Run 5&6 was observed; the step-by-step comparison is not repeated in this discussion for brevity and the reader is directed to the computed data in Table 5.2.

Proceeding to the analysis of the Damkohler number, the first step was to evaluate the computation of the induction time scale. Mannitol is fast to crystallize material and in view of the high crystallinity of the particles produced, the induction time scale should at least be in the same order of magnitude or small than that evaporation time scale. From Table 5.2, based on this reasoning, the computed induction timescale for all the cases seemed logical. Using the computed induction timescale, two sets of Damkohler numbers were evaluated based on the wet bulb temperature and the ‘1/3’ estimation of the droplet temperature described in the preceding section. Usage of the 1/3 estimation provided larger differences and higher sensitivity between the runs. In contrast, the magnitude and differences in the calculated modified-Damkohler number for each experimental case with the wet bulb temperature estimation were smaller. Despite these differences in sensitivity, both computations resulted in the similar trend. A larger modified-Damkohler number, delineating a longer crystal growth time relative to the induction time, resulted in larger and coarser crystals and vice versa. Incorporation of the nucleation and growth behaviour of mannitol in the computation, via the calculation of the induction time in the modified-Damkohler number, also alleviated the discrepancy for Run 3&4 and Run 5&6 observed in the preceding analysis. The only slight discrepancy observed was that the modified-Damkohler number for Run 6 was slightly higher than that of Run 5. This could be an artefact of the lower sensitivity of the computation when approximating with the wet bulb temperature. It is noteworthy that the modified-Damkohler number computed in Table 5.2 are the upper and lower bound of the possible values characterizing the in-situ crystallization process.

This illustrates the importance of incorporating the crystallization behaviour of the material in undertaking such zero-dimension approximation of in-situ crystallization within the spray dryer.

In addition to the surface structure of the particle, a different polymorph of mannitol was discovered. As XRD spectrum (Fig 5.4) shown, there is a trace of alpha polymorph in mannitol crystal for Runs 4 and 5. Run 4 was carried out in higher concentration, 15%, compared to the other Runs. This is inconsistent with the result of Su et al that higher concentration is required for precipitation of alpha polymorph. Comparison of Runs 4 and 5 shows that the evaporation time for these two cases is significantly different. In addition, the available time for crystallization for Run 5 is almost twice than the Run 4. Considering the Damkohler number for these two runs show relatively similar numbers for both cases, larger than one (based on 1/3 Da calculation in Table 5.2). This could be induced that precipitation of alpha polymorph of mannitol is possible when the kinetics of crystallization is relatively fast. So, the shorter induction time could be achieved in higher drying temperature accelerate the kinetics of crystallization before moisture content is significantly reduced. Although the XRD spectrum show the trace of alpha mannitol, it is not observable in SEM images that could be due low degree of alpha mannitol. Because the Alpha mannitol has very thin needle shape crystal compared to thick needle shape crystal of beta mannitol (Cares-Pacheco, Vaca-Medina et al. 2014).

Conclusion

A theoretical framework was developed to predict the final surface structure of crystalline particles produced via spray drying. The novelty of the current predictive approach was to consider the kinetics of crystallization in addition to the various drying related processing condition. The outcome of the theoretical study was a modified Damkohler number that takes into account the competition between evaporation and crystallization time scales on the overall crystallization process. The result of the model was compared with experimental data to understand the development of surface crystallinity better and subsequently the particle structure observed. From this analysis, higher crystallization kinetics relative to the drying rate results in more distinct crystal formation. More work will be required to further assess this predictive framework for spray drying of materials with varying crystallization kinetics under different spray drying conditions.

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Appendix

5.1.6 Back-calculation from the experiments of Su et al. (Su, Hao et al. 2013)to determine α in Equation (6)

In the experiments by Su *et al.* (Su, Hao et al. 2013), induction time for the precipitation of α-, δ- and β-mannitol was measured by cooling crystallization experiments. Precipitation of α-, δ- and β-mannitol was dependent on the initial concentration of the aqueous mannitol solution used: the highest initial supersaturation led to the precipitation of α-mannitol followed by δ- and β-mannitol as the initial supersaturation was decreased. The induction time of the metastable α- mannitol was also the shortest between the different polymorphs being two magnitudes shorter than that of β-mannitol.

From the XRD and FTIR analysis of our current samples, there seemed to be a mixture of α and β mannitol produced. It is unclear which polymorph was the dominant crystal form produced during the induction period. There are also reports in which the spray drying of the different forms of mannitol polymorphs resulted in the thermodynamically most stable β form due to polymorphic change. Therefore, as a basis, the induction time of α-mannitol in the experiments of Su *et al.* (Su, Hao et al. 2013)was used for the back-calculation. This will then provide a lower bound in the estimation of the induction of the crystallization process accounting for the polymorph which will have the tendency to precipitate earlier. The experimental conditions for this particular run are given Table 5.A1 below.

Table 5-3A. *Experimental measurements by Su et al. (Su et al., 2013) for the precipitation of alpha and beta mannitol*

Initial concentration	supersaturation	T_{ind}(s)	form
0.049	2.92	120	Alpha
0.0246	1.31	22200	Beta

In view that the experiments by Su *et al.* (Su, Hao et al. 2013) involved cooling crystallization experiments using a stirred reactor tank, primary and secondary nucleation (Shoji 2012, Shoji and Takiyama 2012) was considered mathematically captured as follows,

$$J_p = j_a \exp\left(\frac{j_b}{T^3(\ln S)^2}\right) \qquad \text{(A1)}$$

$$J_s = k_b M_T^j \Delta C^b \qquad \text{(A2)}$$

It is noteworthy that the secondary nucleation was considered only for this back-calculation computation to reflect better the experimental conditions reported by Su *et al.* (Su, Hao et al. 2013) ; to obtain the property ε. In the modified-Damkohler predictive framework for spray drying, only homogenous nucleation was considered for nucleation within the droplets. Combining Equation (A1), (A2), (6) and the properties in Table S1, the estimated value of ε is 2.51 x 10^{-3}. This value was then used as a constant as part of the computation of the modified-Damkohler number in this communication. Typical values reported in the literature are in the range of the mannitol that is calculated here (Kashchiev, Verdoes et al. 1991, Schöll, Vicum et al. 2006).

5.1.7 Calculation of the mass transfer coefficient

The mass transfer coefficient was calculated using the Sherwood correlation below,

$$h_m = \left(2 + 0.6\, Re^{1/2}\, Sc^{1/3} \right) \frac{\alpha}{d_p} \qquad \text{(A3)}$$

Where the Reynolds number was computed based on the magnitude of the relative motion between the air and the particle taking the diameter of the particle as the characteristic length,

$$Re = \frac{\rho_b\, d_p \left| v_p - v_b \right|}{\mu_b} \qquad \text{(A4)}$$

The expression for the Schmidt is given below,

$$Sc = \frac{\mu_b}{\rho_b\, \alpha} \qquad \text{(A5)}$$

Table 5-4A. *Model constants and fluid/droplet properties used in the model*

Parameter	Units
Calculation of the total time for evaporation:	
$\dot{m} = h_m A_s(\rho_s - \rho_\infty)$	Kg/s
$Sh = \frac{h_m d_0}{D} = 2 + 0.6Re^{1/3}Sc^{1/3}$	----
$Re = \frac{\rho v d_0}{\mu}$	----
$Sc = \frac{\mu}{\rho D}$	----
$\kappa = \frac{4\dot{m}}{\pi d_0 \rho_{solution}}$	m^2/s
$\rho_{vap,sur} = \frac{P_{sat,H_2O@T_{wb}} M_r}{R_g T_{wb}}$	kg/m^3
$\rho_{amb} = \frac{P_{sat,H_2O@T_{db}} M_r \psi}{R_g T_{db}}$	
$log P_{sat,H_2O@T_{wb}} = A_p - \left(\frac{B_p}{T_{wb}(K) + C_p}\right)$	kg/m^3
	Pa
Calculation of the surface enrichment time:	
$E_i = \frac{c_{s,i}}{c_{m,i}} = 1 + \frac{Pe_i}{5} + \frac{{Pe_i}^2}{100} - \frac{{Pe_i}^3}{4000}$	
$t_{sat} = t_D \left(1 - \left(\frac{c_i E_i}{c_s}\right)^{\frac{2}{3}}\right)$	---
Calculation of the induction time:	S
$t_{ind} = \frac{1}{JV} + \left(\frac{\alpha}{a_n J G^{n-1}}\right)^{1/n}$	
For 1D linear growth $n = 2;\ a_n = A_c$	
	S
$J = A \times exp\left[-\frac{16\pi\gamma^3 v^2}{3K^3T^3(\ln S)^2}\right]$	
$A = 10^{30}$	

$\gamma = 3.23 \times 10^{-3}$	
	m^3/s
$G = K_G e^{-(\frac{\Delta E_g}{RT})} \times \left\{1 - e^{\left(-c_g[L+\beta]\right)}\right\} \sigma^g$	J/m^2
	m/s
$K_G = 2.05 \times 10^5$	
$\Delta E_g = 5.77 \times 10^4$	
$c_g = 7.18 \times 10^2$	m/s
$\beta = 6.1 \times 10^{-5}$	J/mol
$\sigma : (\frac{C^*}{C} - 1)$	
$g = 1.42$	---
	M
$r^* = \frac{f_s \gamma v}{3 f_V K T ln\, S}$	---
	---
f_s=37	
f_V=8.9	M

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Chapter six

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6 Conclusion & Recommendation

Conclusion

The first objective of this study, in Chapter 3, was to investigate possibility of using counter-current spray dryer for manufacturing in-situ crystalline particles. Lactose and mannitol which are typical pharmaceutical excipients were used in this study. In addition, sucrose as a complementary material, which is not easy crystallize, was also used. Therefore, the range of materials evaluated covered materials with different kinetic of crystallization, ranging from mannitol with fast to sucrose with slow kinetic of crystallization. This part of the study revealed that counter current spray drying is a feasible approach to produce spray dried crystalline particles. The main finding was the concept of the effective ‘wet time’ for in-situ crystallization which had to be extended or intensified to produce crystalline particles. High operating temperature can be used to intensify the ‘wet time’ as droplet temperature affects the nucleation behavior of solutes during dehydration; this strategy is important particularly for slow to crystallize materials such as lactose. This part of the study also validated the initial hypothesis in which the less intense initial evaporation rate (due to the initial contact between the droplets and the relatively cooler air) in the counter current spray drying configuration gives a wider control for in-situ crystallization.

In the experimental work to extend the wet time for crystallization, it was found that the humidity in the chamber was a key parameter in the control of in-situ crystallization. Therefore, in Chapter 4, the main aim was to further understand the mechanism in which humidity affects particle formation and lactose, which is a slow to crystallize material, was chosen for the study. Local humidity within the spray drying chamber was manipulated by the injection of hot water (which eventually vaporizes) into specific locations within the chamber during the spray drying operation. It was found that the increase in humidity at the intermediate stage of droplet drying, at the period in which the droplets start to solidify, produced the highest level of crystallinity. This provided more detailed evidence on the need to intensify the ‘wet time' for crystallization which in essence is the period corresponding to the solidification of the droplet. This part of the study also showed that in addition to the solid phase transition, a well-known mechanism for crystallization in spray drying, the liquid phase crystallization should also be taken into account. One strategy to capitalize liquid phase crystallization, particularly for slow to crystallize materials, is to provide sufficient humidity (to extend the wet time) coupled by high operating temperature (to 'intensify' the wet time by directly manipulating nucleation.

Having established the importance of the liquid phase crystallization, in Chapter 5, the study then focused on developing a quick predictive framework for in-situ crystallization in spray drying. Mannitol, which is a fast to crystallize material, was chosen as a model material for this part of the study. A modified Damkohler number based non-dimensional analysis incorporating the kinetics of crystallization (nucleation and growth) was developed. The predictive framework quantifies and gives a relative indication of in-situ crystallization based on the ratio between the time scale for crystallization and the times scale for induction to crystallization during the dehydration process. The developed framework was found to be able to provide relative indications on the degree of crystallization for spray dried mannitol particles, capturing the effect of non-linear interactions between the important operating parameters of spray drying. Different degree of crystallization was also found to result in significant different particle rugosity and in certain drying conditions, significant janus-crystallization behaviour within a single particle was observed.

Recommendation and future work

This study for the first time revealed the potential of a different configuration of counter current spray dryer for manufacturing crystalline pharmaceutical excipients. Manufacturing of crystalline powder with the current design of counter current dryer showed another capability of this configuration. The experiments and studies undertaken in this thesis should be interpreted as an initial step for a wider scope of exploration to manufacture various different engineered crystalline particles. On this basis different strategies could be adopted to unveil the full potential of in-situ crystallization.

This study focused on three main type of sugars which are mostly used as excipient in pharmaceuticals. Therefore, different materials could be spray dried with this type of counter current spray dryer and the feasibility of in-situ crystallization specifically the concept of the 'wet time' should be investigate for different specific materials. In this regards, amino acids may be suitable as a candidate model material. Co-spray drying and mixing feed materials with materials with fast kinetic of crystallization could be another opportunities to be tested for in-situ crystallization.

The in-situ crystallization study undertaken here could also be extended to incorporate additional methods to induce nucleation. This could be undertaken by seeding the feed spray solution. Mixing feed material with a material having a fast kinetic of crystallization could also results in earlier generation of nuclei that could further stimulate the nucleation of material with inferior crystallization behaviour. For example, mixing lactose with mannitol or amino acids with mannitol could be interesting ideas.

At this stage, the feasibility of manufacturing in-situ crystallization via spray drying has been proven. The flowability and functionality of the crystalline (and partially crystalline) particles produced with this method will be of interest to the food and pharmaceutical industries. Therefore, future studies could focus on investigation of the functionality, stability and flowability of the crystalline particles manufactured with this method.

The theoretical framework developed in this thesis should be further developed and evaluated with a wider range of materials with fast kinetic of crystallization. This could be a base model for further development. At this stage, some material specific properties used in model were theoretically calculated; e.g volume of initial nuclei or detectable nuclei. More detailed and more intricate experiments should be developed to allow direct and quick measurements of these properties. In addition, the model will need to be tested for materials that have high tendencies to form different polymorphs. The capability to predict the development of different polymorphs will be a very useful addition to the current predictive framework.