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

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ABSTRACT

In-situ crystallization of particles in spray drying has several advantages particularly for product quality modification in the pharmaceutical industry. This process was investigated in a counter current spray dryer using lactose as a model material by manipulation of the local humidity within the drying chamber. Sample collection and humidity injection at different location of the dryer were carried out to better understand the mechanism of particle formation and solidification which are essential components of in-situ crystallization. They revealed that particle formation can be delayed by local humidity elevation. Differential scanning calorimetry and XRD of the yields showed that humidity manipulation was capable to produce semi crystalline lactose of up to 90% 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.



## 1. Introduction

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

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

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

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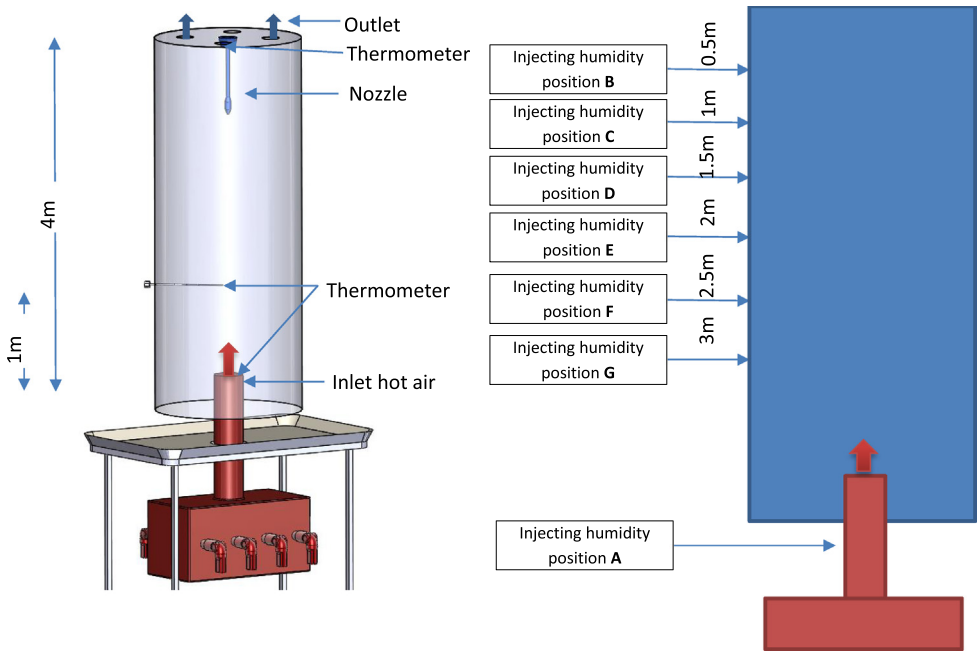


**Fig. 1.** (Left) schematic of the spray drying tower; (right) position of humidity injection and sample collection at different heights of spray dryer.

the moisture enhances the mobility of crystallization forming nuclei through the drying. Although the drying temperature is an important parameter in crystallization, this is only one aspect of a complicated process involving various parameters.

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

## 2. Materials and equipment

### 2.1. Material

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

### 2.2. Experimental equipment

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

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

**Table 1**
Spray dried lactose 10% (w/w) in various processing conditions.

| Run | Humidity injection | Absolute humidity inlet/outlet (g/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% |