

Demonstrating the link between spray drying and single droplet drying for two organic, crystalline aqueous solutions, 22nd International Drying Symposium (IDS 2020)

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Abstract

Single droplet drying (SDD) is a small scale technique that has the potential to reduce the costs associated with developing a spray drying process. The drying behaviour of aqueous solutions of two organic, crystalline materials, L-glutamic acid (0.6 wt%) and choline bitartrate (30 wt%), have been assessed using a SDD technique and then compared to the results obtained from a pilot-scale spray dryer. A link in drying behaviours across the two scales has been demonstrated and it has been shown how SDD could be used for predictions of particle morphology and amount of deposition and agglomeration.

Keywords: Spray drying; Single droplet drying; Particle formation



1. Introduction

Spray drying is used in a wide variety of manufacturing industries, and its wide usage can be attributed to its dual-functionality – the primary drying function and a secondary particle engineering function [1]. Spray drying is also an established continuous manufacturing technique, which makes it well-placed for use within the pharmaceutical industry's move towards continuous processing.

The spray drying process can be broken down into 4 key stages: feed, atomisation, drying and product recovery. The fundamentals of a spray drying process have been described in detail in previous work [2]. A feed solution or slurry is atomised to produce a fine, high surface area, spray. This spray encounters a heated gas stream causing droplet drying. As the droplets dry, their solute concentration increases until, at a critical point, a particle forms. The dried particles are then typically separated from the gas stream using cyclones and/or bag filters.

The drying step within a spray dryer is complicated and depends on gas conditions (composition, flow rate, temperature and relative humidity) and on the droplets/particles (solvent, solute or suspended material, concentration and droplet size). The wide range of factors enables a large variety of particle morphologies to form during a spray drying process [3] with different morphologies being desirable for different applications.

The complicated drying step makes the unique selling point of the spray drying process, engineering particle properties during drying, a challenge. It is often difficult to find the process conditions that produce the desired final particle. Typically, numerous large-scale experiments are required to predict the dried particle properties. This is expensive, especially in pharmaceutical applications where raw materials are costly.

One option to try and reduce the number of large-scale experiments that are required, is the use of single droplet drying (SDD), a small-scale technique, to obtain information about particle morphological development and drying kinetics. In SDD a single droplet is isolated in variable drying conditions, allowing for detailed measurement of the drying rate and observation of any morphological changes that occur. There are a number of different SDD techniques (varying in the way droplets are isolated) [4], which have been used extensively in the past to better understand droplet drying behavior. There is, however, still some uncertainty in how well the drying behavior observed at the smaller scale, where drying conditions and droplet sizes are often significantly different, match the drying behaviours within full-scale spray dryers. There have been attempts to investigate this [5–7], but a consensus has not been achieved and further work is required in this area.

The aims of this work were (1) to investigate the drying behavior of aqueous solutions of two organic crystalline materials, L-glutamic acid (LGA) and choline bitartrate (ChB) and (2) to compare the drying behaviours between single droplet drying and a pilot-scale spray dryer. The materials were chosen due to their similarity to pharmaceutical materials, whilst being unhazardous. The solution concentrations were close to the materials solubility limits, as is the general practice within industry.



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2. Materials and Methods

2.1. Materials

L-Glutamic acid (LGA) from Sigma-Aldrich (purity 99 %) was used to make 0.6 wt% solutions. Choline bitartrate (ChB) from Alfa Aesar (purity 98+%) was used to make 30 wt% solutions. Both used de-ionised water obtained from a Millipore ultra-pure system.

2.2. Methods

2.2.1. Suspended droplet drying

Suspended droplet drying was performed on the custom-built rig shown in Figure 1. A single droplet (around 1 .5 mm in diameter) was suspended from a 0.2mm, polyetheretherketone (PEEK) filament or from a 0.075 mm, type K thermocouple. A conditioned hot air flow, where the temperature and velocity can be varied, was passed across the droplet. Twenty-four mesh screens (perpendicular to the airflow) were used before the droplet location in order to flatten the air velocity profile and minimise the movement of the droplet during drying. The drying air had a relative humidity of 0 % and was set to a temperature of 65 °C and a velocity of 0.6 m/s. The evaporation rate of the droplet and morphological changes were observed using a camera and an appropriate light set-up. The diameter of the droplet as the experiment progressed was measured offline using ImageJ 2.0.0 software.



Figure 1 - Suspended droplet drying rig developed at the University of Leeds, including schematic of drying droplet

2.2.2. Spray drying

Spray drying experiments were performed using a ProCept spray dryer [8] which was used in its three-column set-up, where it has a height of 1.8 m. An ultrasonic atomiser nozzle with a frequency of 25 kHz and set at 80 % power (approx. 3W) was used for atomisation. At the conditions used, the D(10), D(50) and D(90) values of the droplets were approximately 50 μ m, 80 μ m and 130 μ m (based on volume). Three inlet temperatures were used (100 °C, 140 °C and 200 °C) with a drying air flow rate of 0.4 $\frac{m^3}{min}$. The peristaltic pump was maintained at a constant value which produced a feed mass flow rate of around 3.5 g/min.



2.2.3. X-ray tomography (XRT)

XRT was performed at the Diamond Light Source on beamline I13-2 - Manchester Imaging Branchline [9].

2.2.4. Scanning Electron Microscopy (SEM)

A Hitachi benchtop SEM TM3030 plus was used to investigate the morphology and size of particles produced in the spray drying experiments.

3. Results and Discussion

3.1. Suspended droplet drying



Figure 2 - Diameter (left) and temperature (right) profiles of suspended aq. ChB (30 wt%) and aq. LGA (0.6 wt%) droplets during drying (65 °C and 0.6 m/s)

Figure 2 shows the diameter and temperature profiles of the suspended aq. ChB (30 wt%) and aq. LGA (0.6 wt%) droplets during their drying time. From the diameter plot, it can be seen that the drying rate of the aqueous ChB droplet was significantly slower than the aqueous LGA droplet. The temperature profile of the LGA droplet shows that it spent practically its entire drying time at its wet bulb temperature, highlighting it was in the constant drying period, which represents the fastest possible drying rate for a particular solvent and drying conditions. The aqueous ChB droplet spends almost no time in the constant drying period and starts steadily increasing in temperature early on in its drying time. This shows that the droplets drying rate is continuing to decrease as drying continues, highlighting that the droplet has entered the hindered drying period. As the droplet dries the solute concentration at the droplet surface increases, which causes vapour pressure lowering, reducing the drying rate. At a certain point a solid crust forms, which limits the transfer of moisture from the droplet centre to the surface, further reducing the drying rate. The mechanical properties of the formed crust plays a large role in determining the final particle morphology. The particle's moist centre dries further as moisture is transferred across the crust and evaporated. This causes the crust to thicken and eventually leaves a hollow final structure.

During the suspended droplet drying, the LGA droplet climbed the suspending filament, causing the final particle morphology to be disrupted. However, the SDD results showed that a particle was formed at the very end of drying, with no hindered drying period. This shows



that there was no solid crust formation, and a small, solid final particle would be expected. The ChB droplet entered the hindered drying period early on in its drying history and as has been mentioned, this makes a hollow final particle structure probable.

The predicted hollow structure for the ChB particles was confirmed using XRT, as is shown in Figure 3. The central void was not spherical in shape, but had a number of straight edges, indicating the possible presence of crystals. The long drying time due to the large droplet size provided a long period of growth for the crystals, which allowed them to attain a large enough size to impact the shape of the central void.



Figure 3 – XRT cross-sections of the centre of a suspended droplet dried particle of ChB

3.2. Spray drying

Figure 4 shows SEM images of the LGA and ChB as-received powder, and the spray dried powders of the aqueous solutions at the various inlet temperatures that were used. X-ray diffraction results showed that both the as-received powders and the spray dried powders for both materials were crystalline in nature.

The LGA from the supplier was in the beta form (needle shaped crystals). For the spray dried powders, it can be seen that even at 100 °C inlet air temperature, the LGA was able to form spherical particles. The particles had a rough surface as the low air temperature led to a slow drying rate. The slow drying rate kept the supersaturation within droplets low which allowed the formation of large crystals as crystal growth prevailed over nucleation. There was also some agglomeration between particles which would be consistent with partially dried particles sticking together. As the inlet air temperature increased, increasing the drying rate, the particles' surfaces became smoother due to smaller crystals forming inside the droplet, and less particle agglomeration occurred. At the highest inlet air temperature (200 °C), it can be seen that the particles are very spherical, with a smooth surface, where individual crystals were too small to identify. Observations made during the spray drying process highlighted that, although the amount of wall deposits in the spray dryer was low for all of the runs, it did decrease as the inlet air temperature was increased.

For the ChB, the as-received powder from the supplier appeared to consist of agglomerates of smaller crystals. For the spray dried powder, at the lowest inlet air temperature, no spherical particles were observed but there were instead, large agglomerates. During the spray drying process, there was a significant amount of deposition of solid particles in the transfer tube, between the bottom of the spray dryer and the separation cyclone. The low drying temperature meant droplets could not dry suitably in the residence time of the spray dryer. After impacting on the transfer tube, the solution droplets dried and caked its walls. The airflow within the dryer then caused caked material to break away from the deposit and be collected. Interestingly, in other experiments (not shown in this paper), where a 20 wt% solution of ChB was used, distinct particles were able to form at the 100 °C inlet temperature,



although there was significant agglomeration. The higher concentration of ChB must decrease the droplets drying rate, preventing the formation of dry particles in the residence time of the dryer. This is likely due to earlier crust formation or increased vapour pressure reduction due to higher surface solute concentration.



Figure 4 - SEM images of (left) LGA and (right) ChB: (a) as-received from supplier; spray dried: (b) 100 °C inlet temp; (c) 140 °C inlet temp; (d) 200 °C inlet temp.

As the spray drying inlet air temperature was increased, it can be seen in Figure 4 that spherical particles started to form but with a significant amount of agglomeration. This shows that the droplets were able to dry to form particles, but the particles were still moist and sticky when they collide with each other, causing agglomerates to form. At the higher drying temperatures, a significant amount of deposition built-up on the temperature probe (situated on the exit air stream), reducing the process yield. This highlighted that a large number of the particles were not suitably dry when they were leaving the drying chamber. Break-offs from this deposit caused the larger agglomerates that are seen in Figure 4 (c) and (d).

Figure 5 shows XRT cross-sections of spray dried (200 °C inlet air) LGA and ChB particles. It can be seen that the LGA particles were smaller and had a solid structure with minimal agglomeration. The ChB particles displayed significant agglomeration, with the largest agglomerates being deposit breakoffs, but the primary particle size was still larger than obtained with LGA. The internal structure of a significant number of the primary particles contained voids, demonstrating they had a similar structure to the ones produced using suspended droplet drying. The void spaces in the spray dried particles appeared to be more spherical than the ones seen in the suspended dried particles. This was likely due to the much faster drying times of the spray dried particles which caused smaller crystal sizes. These smaller crystals were able to fit together more coherently and did not intrude into the central



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void like the larger crystals in the suspended dried particles. The void space, compared to the overall particle size, was also larger in the spray dried powder which was expected as the faster drying rate leads to a larger build-up of solute at the droplet surface causing crust-formation to occur earlier.



Figure 5 – XRT cross-section of spray dried (200 °C inlet air) (left) LGA, (right) ChB

3.3. Comparisons of drying behavior across scales

The suspended droplet drying results showed that aqueous ChB (30 wt%) had a significantly slower drying rate than aqueous LGA (0.6 wt%) due to the ChB solution entering the hindered drying period early on in its drying time. ChB had a much larger solution concentration due to its significantly higher aqueous solubility. During drying, both solutions reached supersaturation levels soon in their drying history. The high solute concentration in the ChB solution meant, when crystallisation occurred, the crystals had a high concentration. This allowed them to influence the droplet's structure and form a solid phase on the droplet's surface. This influenced the droplets drying behaviour, causing a reduced drying rate and a hollow final structure, as seen in XRT images. The low solute concentration in the LGA solution meant, when the crystals formed within the droplet, they were sparse and surrounded by water. They were unable to form a continuous phase until the droplet had dried significantly, and subsequently; the droplet dried very similar to a pure water droplet for almost its entire drying time.

The longer drying time observed for the ChB suspended droplet, agreed with spray drying results, which showed the ChB required a higher inlet air temperature to form particles. The ChB solution also caused significantly more deposits in the dryer and there was increased agglomeration. The expected spray dried particle structures from the suspended droplet drying (solid for LGA and hollow for ChB), were observed in the x-ray tomography images of the spray dried powders. This shows that, even though the droplets used during suspended droplet drying were significantly larger than the spray dried droplets, drying behaviours observed during suspended droplet drying did inform on spray drying behaviours.

4. Conclusions

A link between the drying behavior of spray drying and single droplet drying has been demonstrated for aqueous solutions of two organic, crystalline materials, L-glutamic acid and choline bitartrate. The drying behaviours of the solutions (0.6 wt% L-glutamic acid and 30 wt% choline bitartrate) were substantially different, leading to different particle



morphologies and levels of agglomeration and deposition. Both solutions were at close-tosaturation conditions, but choline bitartrate has a much higher aqueous solubility, which led to a much larger solution concentration at equivalent saturation temperature. This higher concentration caused a significantly lower drying rate due to vapour pressure lowering by the solutes and earlier crust formation, which added a mass transfer resistance to moisture leaving the particle. This earlier crust formation also caused a hollow particle structure, whereas the L-glutamic acid particles were solid.

The different drying behaviours of the solutions were observed at single droplet drying scale and matched the behaviours seen during spray drying. These results have demonstrated the predictive capabilities of single droplet drying and the following drying behaviours, which were confirmed by spray drying experiments, were able to be predicted before any spray drying experiments were performed:

- Choline bitartrate's slower drying rate means:
 - It will require a higher drying temperature to form particles
 - \circ It will have higher rates of agglomeration and deposition
- Choline bitartrate will have a hollow particle structure
- L-glutamic acid will have a solid particle structure

5. References

- Al-Khattawi, A.; Bayly, A.; Phillips, A.; Wilson, D. The Design and Scale-up of Spray Dried Particle Delivery Systems. *Expert Opin. Drug Deliv.*, 2017, 15 (1), 47– 63. https://doi.org/10.1080/17425247.2017.1321634.
- [2] Masters, K. Spray Drying: An Introduction to Principles, Operational Practice and Applications; Leonard Hill Books: London, 1972.
- [3] Walton, D. E. The Morphology of Spray-Dried Particles a Qualitative View. *Dry. Technol.*, **2000**, *18* (9), 1943–1986. https://doi.org/10.1080/07373930008917822.
- [4] Fu, N.; Woo, M. W.; Chen, X. D. Single Droplet Drying Technique to Study Drying Kinetics Measurement and Particle Functionality: A Review. *Dry. Technol.*, 2012, 30 (15), 1771–1785. https://doi.org/10.1080/07373937.2012.708002.
- [5] Nuzzo, M.; Sloth Overgaard, J.; Bergenståhl, B.; Millqvist-Fureby, A. The Morphology and Internal Composition of Dried Particles from Whole Milk—From Single Droplet to Full Scale Drying. *Food Struct.*, **2017**, *13*, 35–44. https://doi.org/10.1016/j.foostr.2017.02.001.
- [6] Ullum, T.; Sloth, J.; Brask, A.; Wahlberg, M. Predicting Spray Dryer Deposits by CFD and an Empirical Drying Model. *Dry. Technol.*, **2010**, *28* (5), 723–729. https://doi.org/10.1080/07373931003799319.
- [7] Littringer, E. M.; Paus, R.; Mescher, A.; Schroettner, H.; Walzel, P.; Urbanetz, N. A. The Morphology of Spray Dried Mannitol Particles The Vital Importance of Droplet Size. *Powder Technol.*, 2013, 239, 162–174. https://doi.org/10.1016/j.powtec.2013.01.065.
- [8] ProCept. Spray Dryer / Chiller | ProCepT http://www.procept.be/spray-dryer-chiller (accessed Aug 17, 2020).
- [9] Diamond Light Source. I13 X-Ray Imaging and Coherence Materials Diamond Light Source https://www.diamond.ac.uk/Instruments/Imaging-and-Microscopy/I13.html (accessed Jul 20, 2020).



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