

Navigating the Spray Drying Process: Impact of Bulking Excipients on Nasal Powder Manufacture and Process Scalability

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Summary

Spray drying is a widely used platform in the manufacture of inhaled pharmaceutical products, with growing interest in its application for vaccines and biologics intended for intranasal delivery. Recent efforts focus on improving shelf-life stability and expanding the global availability of vaccines for nasal administration. This study seeks to optimize the spray drying process for intranasal formulations, with a particular focus on the role of bulking excipients.

Introduction

This study investigates the impact of various bulking agents on the manufacture of nasal powders using ultrasonic atomization, with a particular focus on the scalability of spray drying processes. A primary objective is to achieve the optimal particle size distribution for nasal delivery, while minimizing fraction below 10-micron below 10%, which is a critical quality attribute for nasal powders [1].

In spray drying solutions with higher solids content (targeting a Dv50 of ~25–30 μm), bulking agents play a critical role as key components of the feed solution. Their physicochemical properties significantly influence process development, especially when spray drying from aqueous solutions. This introduces unique challenges due to the higher heat capacity of water, which affects the drying kinetics. These considerations are particularly important for biotherapeutics, which are increasingly being explored for nasal delivery, offering new avenues for the administration of biologic drugs. The goal was to establish a process space and scalability, while enhancing efficiency and throughput for the spray drying process.

Methods

Aqueous solutions were composed of a single excipient at a time. The solutions were representative of feedstock solutions for spray drying nasal powder. The excipients selected for this study were trehalose, HPMC 603, and HPMC 606, chosen for their unique properties that make them ideal bulking agents. The varying viscosities of these excipients are expected to significantly impact atomization, droplet formation, drying kinetics, particle formation, and, ultimately, yield. A wide range of solids content (5, 20, 33wt% trehalose, and 0.5, 2.5 and 5wt% HPMC 606 and 603), and flow rates (0.5, 2.5, and 5.0 g/min) that are relevant for spray drying intranasal powder were explored.

The dynamic viscosity of each solution was measured using a viscometer (Anton Paar ViscoQC 3000), mapping a feasible range of viscosity for atomization and ideal plume formation. These parameters were assessed both visually and through droplet size distribution measurements. Two ultrasonic atomizers were used in the study: a 25 kHz (Sinaptec) and a 60 kHz (SonoTek). The droplet size distribution (DSD) of the plume generated by the 60 kHz atomizer was collected and characterized using a laser diffraction system (Malvern SprayTec). DSD measurements were taken at a 5.0 cm vertical distance from the atomizer tip, with the atomizer positioned equidistantly from the laser and receiver windows (25 cm). The 5 cm vertical distance was selected as it corresponded to a stable region of the generated plume, which was found to be optimal for sizing. The atomization power required to achieve a visually stable plume was optimized for each case.

Spray drying was performed for trehalose aqueous solutions using a PROCEPT dryer (4M8-Trix), equipped with an extended dryer body in a closed loop under N_2 . The drying gas flow rate was set to 0.4 m^3/min to increase the residence time and provide sufficient drying capacity for formulations with high solids content and larger droplet sizes. The column outlet temperature was set to ~70°C, which was found optimal for drying the intranasal powder and suitable for the excipients. The inlet temperature was adjusted accordingly to achieve this condition. The spray dried powders underwent secondary vacuum drying at 40°C for about 48 hours, which was found necessary to remove residual water from intranasal powders. Yields were calculated immediately after collecting the powder in a moisture-controlled environment. The geometric particle size distribution (PSD) was measured at 2.0 bar dispersive pressure using a laser diffraction system (Malvern Mastersizer 3000).

Results

Hydroxypropyl Methylcellulose (HPMC) aqueous solutions were prepared using the 606 and 603 grades at varying concentrations (0.5–10 wt%). The maximum feasible solids content in water was found to be approximately 10 wt%. At 10 wt%, HPMC 603 exhibited a dynamic viscosity of 79.3 cP (Figure 1). HPMC 606 resulted in a significantly higher dynamic viscosity at 10 wt% solids, exceeding the maximum torque capacity of the viscometer, as indicated by the exponential fitting. As a result, both HPMC formulations achieved atomization only at up to 5 wt% solids and failed to atomize effectively at 10 wt%. This limited the use of the 60 kHz ultrasonic atomizer for HPMC solutions to a maximum of 5 wt% solids across a practical range of flow rates. In comparison, aqueous trehalose solutions showed only a marginal increase in viscosity with increasing solids content, ranging from 1–3.8 cP between solutions prepared at 5–33 wt% solids.

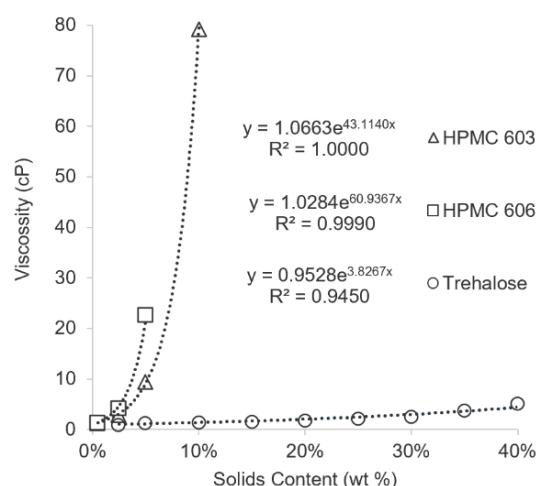


Figure 1: Dynamic viscosity of trehalose, HPMC 603, and HPMC 606 solutions at various concentrations. An exponential fitting was applied to each dataset.

The DSD was measured for each solution atomized using a 60 kHz ultrasonic atomizer at varying flow rates. The Dv10, Dv50, and Dv90 values were plotted as a function of solids percent in solution and the atomization flow rate (Figure 2). A positive correlation between flow rate and droplet size was observed for both trehalose and HPMC. While no clear relationship between solids content and droplet size was evident for trehalose, a strong positive correlation was seen with both HPMC 603 and HPMC 606. The lack of an evident relationship between the DSD and solids content in the trehalose solution is not surprising, as the viscosity remains relatively consistent across the solids range, 5–33 wt%. In contrast, the viscosity of HPMC solutions shows a significant increase at solids content between 0.5–10 wt%. Ultimately, atomizing the trehalose solution at the highest solids concentration (33 wt%) would enable 6.6-fold higher throughput compared to spray drying HPMC solutions at 5 wt%.

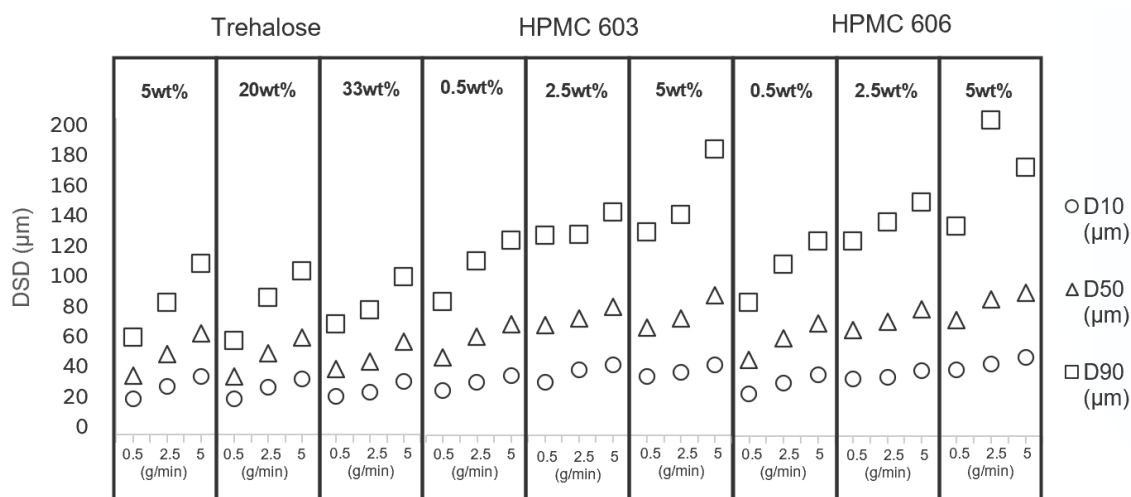


Figure 2: The droplet size distribution (Dv10, Dv50, and Dv90) at various solids content and flow rate for aqueous solutions; trehalose (a), HPMC 603 (b), and HPMC 606 (c). The data is presented as an average of 30 s measurement.

The PSD of spray-dried trehalose solutions at various solids concentrations (5, 20, 33 wt%) and feedstock flow rates (0.5, 2.5, 5.0 g/min) are shown in Figure 3. The PSD is plotted as Dv10, Dv50, and Dv90 as a function of solids content in the feed solution and flow rate. In Figure 3 (a), particle size shows a positive trend with both solids content and flow rate. In Figure 3 (b), the respective yield of powder for each run generally decreased as a function of flow rate for each formulation. However, no clear correlation between solids content and yield was observed, indicating the existence of an optimal process space that allows successful spray drying at higher solids and flow rates, enabling scale-up with higher throughput.

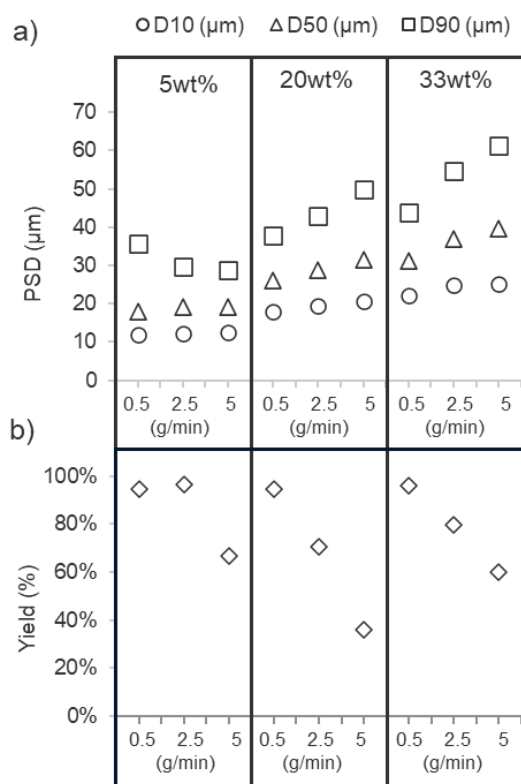


Figure 3: (a) Dv10, Dv50, and Dv90 and (b) yield of spray dried trehalose powder at various solids content and flow rate.

By utilizing the density of a given formulation and the water content of the dried particles, the predicted PSD is based on the measured DSD of the plume generated by the 60 kHz atomizer. The predicted PSD of the powder is compared to the measured PSD of the spray-dried powder with a 25 kHz atomizer, as shown in Figure 4. The comparison demonstrates a good correlation, with R-squared values of 0.98, 0.99, and 0.98 for Dv10, Dv50, and Dv90, respectively.

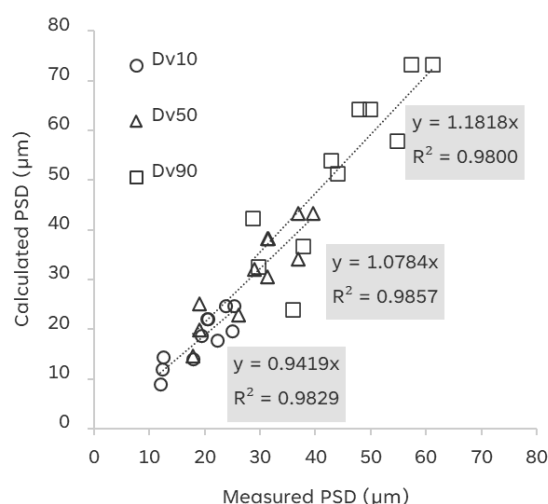


Figure 4: Calculated PSD based on the DSD of the generated plume vs measured PSD of spray dried powder.

The drying kinetics are influenced by inlet temperature and drying gas flow rate. Optimizing the gas flow rate is crucial for maximizing residence time and maintaining adequate heat capacity. At a constant outlet temperature, yield decreases with higher drying gas flow rates due to shorter residence times. Conversely, lower gas flow rates require higher inlet temperatures to achieve the same outlet temperature. Figure 5 shows that as drying gas flow rate increases, yield decreases and inlet temperature needs to be reduced to maintain the desired outlet temperature.

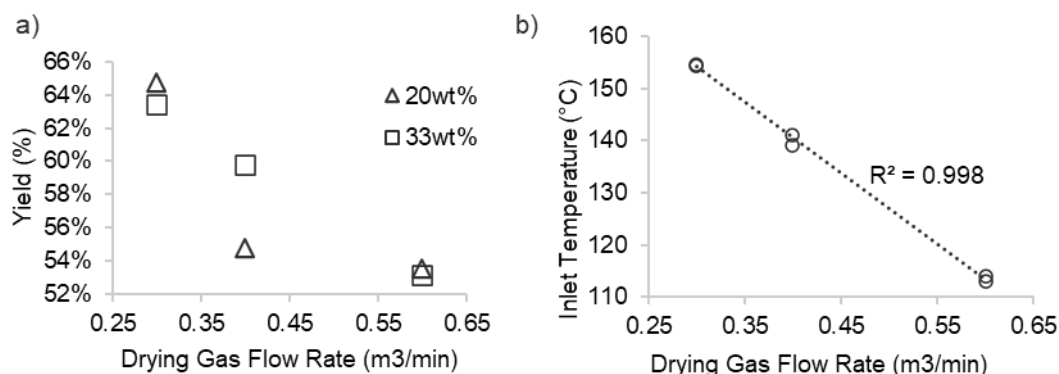


Figure 5: (a) yield and (b) inlet temperature vs the drying gas flow rate, targeting a constant outlet temperature.

Discussion and Conclusions

The choice of excipient is crucial for atomization and droplet formation, as different excipients exhibit varying intermolecular interactions at different concentrations. Non-reducing sugars like trehalose are ideal for spray drying biotherapeutics, as stabilizer for biological entities, glass former, and bulking

agents [2]. Various grades of HPMC, commonly used in spray drying for multiple routes of administration, offer desirable physicochemical properties. They excel at modifying release profiles and enhancing mucoadhesion, while also acting as effective thickening agents for intranasal powders due to their higher viscosities. Higher viscosity results in larger droplets, as it limits stream breakup during atomization. Excipients like HPMC, with higher viscosity, require more energy to overcome atomization resistance, leading to larger droplets. In high solids formulations, binders like HPMC create viscous stresses that exceed the inertial stress from the ultrasonic atomizer, limiting efficient throughput.

Aside from viscosity, the droplet size distribution of the generated plume is also strongly influenced by the atomization flow rate. At higher flow rates, the generated droplets are larger due to the same inertial stress acting on a larger volume of liquid [3]. Ultimately, viscosity and flow rate are the main factors driving droplet formation and, consequently, the formation of larger particles.

Spraying at higher solids content significantly increase throughput while achieving the target PSD for intranasal powders. At higher feed flow rates, the DSD of the generated plume increases, yet the PSD of the spray-dried powder still tracks closely with the solids content of the solution. Once the plume size is optimized for sufficient drying, the PSD aligns with the target intranasal powder size, as the remaining solids in the droplet determine the final particle size. When the process is optimized for complete drying, particle size increases proportionally with both flow rate and solids content due to density. However, incomplete drying from larger droplets causes significant losses, suggesting an upper limit to the DSD for the spray drying process. A strong correlation exists between DSD and PSD, primarily driven by solids content and predicted water content in the dried powder.

Optimizing drying kinetics required fine-tuning both the drying gas flow rate and inlet temperature. A higher drying gas flow rate led to a decrease in inlet temperature, necessary to maintain an optimal column outlet temperature of 65°C. However, this also resulted in shorter residence time within the dryer, which ultimately decreased yields. A drying gas flow rate of 0.4 m³/min was identified as optimal on the spray dryer, improving both drying efficiency and throughput while maintaining reasonable residual water content, particularly for spray drying intranasal powders with higher solids content. These results highlight the importance of optimizing the process space for higher throughput while maintaining the critical product quality attributes for intranasal-sized powders.

References

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