

Novel Use of a Modified Ink-Jet Print Head to Produce Spray-Freeze Dried Particles for Inhalation

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Summary

Small quantities of lactose in solution have been sprayed into liquid nitrogen from a thermal ink-jet printer cartridge. Following freeze-drying, the particles were shown by electron microscopy to be porous and spherical in nature. Changing the print quality had no effect on the particles produced but increasing the feed concentration caused an increase in particle size.

Thermal ink-jet printing has been shown to be suitable for preparing particles for inhalation by spray-freeze drying (SFD). The small quantities of material required, allow the SFD approach to be evaluated early in preformulation.

Introduction

There are many methods available with which to produce particles suitable for inhalation; a representative selection would include milling, controlled crystallisation, spray-drying and spray-freeze drying (SFD). Spray drying is widely used as it produces spherical particles in the 2-5 μm range required for delivery to the lower respiratory airways. SFD is an alternative approach where solutions are atomised into liquid nitrogen; the frozen particles are subsequently freeze-dried to produce spherical material with an extremely porous structure. In either case, the quantity of feed material required can be substantial, even on the laboratory scale, which means evaluation of spray-drying or SFD early in the development process can be problematic if the material is available only in limited quantities.

Thermal ink-jet technology can produce droplets in the range of 6 to 10 μL (equating to 10-12.5 μm diameter spheres) with tight control over droplet size distributions [1] from very small (less than 5 μL) reservoirs of solution. Porous particles produced at ca. 10-12 μm may express an aerodynamic profile within the respirable particle size range (1-5 μm) [2]. Hence, thermal ink-jet technology appears to have the potential to be able to manufacture SFD particles for inhalation using very small quantities of feed material. Demonstration of the utility of the technology for this application is the focus of this study.

The specific aims and objectives were thus;

- To assess the potential to produce small-scale batches of SFD materials
- To determine the ability to control droplet/particle size by manipulating the modified printer head spray system, using lactose as a model excipient
- To assess the effect of feed concentration on the particles produced, using lactose as a model excipient

Materials and Methods

α -lactose monohydrate was purchased from Sigma-Aldrich (UK). Solutions were prepared in deionised water.

Solutions were printed using a modified Hewlett-Packard Deskjet 340 printer. Modifications were made in accordance with those in [3]. Briefly, the ink-jet printer was modified so that the print cartridge could be held externally from the printer body, over a beaker of liquid nitrogen. The top of the printer cartridge was cut off and the ink removed. This allowed the solution to be printed to be poured in. To initiate an experiment the printer was instructed to print a black page; this turned on droplet production at the ink-jet head. Lactose solutions were prepared at a range of concentrations (5, 10 and 15 % w/v) and transferred to the printer cartridge for printing. Droplets were printed into liquid nitrogen, filtered, collected and kept in a freezer (-20 °C) prior to being freeze-dried (Advantage Lyophilizer, Virtis Inc).

Moisture content of the SFD particles was determined with thermogravimetric analysis (Pyris 6, Perkin Elmer). Samples (2-4 mg) were loaded into open aluminium pans and allowed to reach equilibrium at 30 °C. Samples were then heated at 10 °C min⁻¹ to 200 °C.

The physical form of the SFD particles was determined with differential scanning calorimetry (either Pyris 1, Perkin Elmer or RHC, TA Instruments). Samples (ca. 10 mg, Pyris 1 or ca. 0.1 mg, RHC) were loaded into hermetically sealed aluminium pans and allowed to reach equilibrium. Samples were heated at 10 °C min⁻¹ from -60 to 200 °C (Pyris 1) or at 1000 or 1250 °C min⁻¹ from -190 to 250 °C (RHC).

SFD particle size distributions were determined with laser diffraction (Mastersizer, Malvern Instruments Ltd).

Results and discussion

Spray-freeze drying lactose produced spherical particles that were extremely porous in nature (the electron micrograph image in Figure 1 shows particles produced from a 15% w/v solution). All samples had water contents of between 3-5 % w/w. Although the particle size in the image is greater than that needed for inhalation (ca. 70 μm), the average particle size data were lower (see Table 1) and it is also likely that the aerodynamic particle size of this material will be smaller (this will be determined in future work).

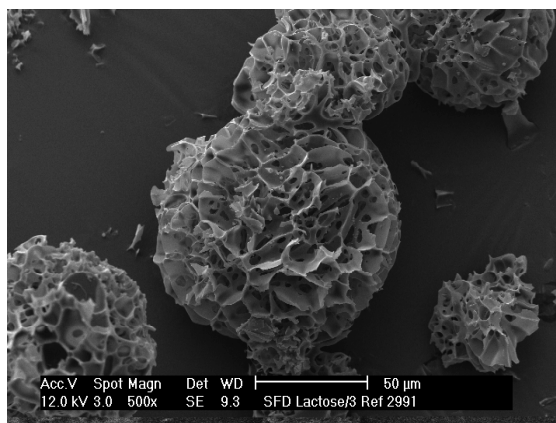


Figure 1: An electron micrograph of the particles produced by spray-freeze drying lactose from a 15% w/v feed solution.

DSC data showed the SFD material to be amorphous, as indicated by the presence of a glass transition. At fast heating rates (1000 and 1250 $^{\circ}\text{C min}^{-1}$), glass transitions were seen at ca. 44 $^{\circ}\text{C}$. At slow heating rates (10 $^{\circ}\text{C min}^{-1}$) glass transitions were seen at ca. 120 $^{\circ}\text{C}$. The explanation for these differences is as follows. Water acts as a plasticiser for amorphous lactose. At the slower scan rate the sample loses its water as it is heated and the glass transition temperature corresponds with that of dry amorphous lactose (ca. 116 $^{\circ}\text{C}$). At the faster heating rates the sample reaches the glass transition temperature before the water can evaporate and hence a 'plasticised' glass transition temperature is recorded. The fact that the measured glass transition temperature did not move with increasing scan rate implies that the instrument response is faster than the sample response and hence 44 $^{\circ}\text{C}$ is the 'true' plasticized transition temperature (See [4] for further details). These observations are of importance because to store SFD lactose over an extended period of time it is necessary to ensure that the storage temperature is considerably below the glass transition temperature, which is ca. 44 $^{\circ}\text{C}$ in this instance. The effects of two experimental parameters on the nature of the particles produced were investigated; feed concentration and print quality. Feed concentrations were prepared at 5, 10 and 15% w/v while material was printed using 'economical', 'normal' and 'best' modes. The particle size data are given in Table 1.

Print quality	Average particle size ($D_{v,50}$ / μm)		
	5 % w/v feed	10 % w/v feed	15 % w/v feed
Economical	11.8 \pm 2.0	16.9 \pm 0.7	20.3 \pm 1.1
Normal	11.3 \pm 1.2	13.6 \pm 1.2	16.7 \pm 1.0
Best	10.4 \pm 2.3	15.2 \pm 2.3	18.3 \pm 1.2

Table 1: Particle size data for SFD lactose as a function of feed concentration and print quality (n=5).

The particles produced are of a size consistent with that expected of the drop size, which suggests that one drop results in formation of one particle. It is apparent that altering print quality did not impact particle size whereas increasing feed concentration caused an increase in average particle size. This suggests that the printer alters the rate of droplet production to control image resolution rather than modulating the droplet size. The data also suggest that there is some degree of control over particle size possible by manipulating the experimental parameters.

Summary

The preliminary investigation of the technology combination has successfully demonstrated that highly porous particles can be produced within the expected geometric particle size range (ca. 10µm). Further work is required to determine if the particles are sufficiently porous to yield materials suitable for use in an inhalation formulation. There is a need to evaluate the effect of adding water soluble API's to the formulation and the impact this has on particles size and morphology. Future studies incorporating API's into the formulation will focus on the anticipated amorphous nature of the particles produced and the stability of these materials as a function of time. Different excipients and excipient combinations may need to be examined to provide stability.

Future Areas of Investigation

- To produce materials using a range of pharmaceutical excipients to correlate physical changes in the particle's morphology with the excipient(s) used and the solute content.
- To examine the aerodynamic performance of SFD particles by cascade impaction to relate geometric particle size with aerodynamic particle size and define the geometric particle size needed for impaction within the respirable particle range.
- To explore the potential to use mercury porosimetry to assess the particles' envelope density (specific particle density inclusive of voids and pores) which in combination with geometric particle size may allow prediction of aerodynamic particle size.
- To assess the print head's capability to spray materials dissolved in alternate or co-solvents, thus allowing for non water soluble materials to be produced and assessed.

It is noted that the lack of any heating processes in the production of SFD particles has the potential to allow for incorporation and delivery of a diverse array of APIs including heat labile biologics.

References

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