A Spray Dryer Method for the Micronization of Small Amounts of Substance in High Yield for Aerosol Generation

Inhalation Sciences

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Background

In early drug development and chemical synthesis new substances are available only in small amounts, and there is often need for obtaining the substance in a pure and solvent-free form. Spray drying is one important method to produce easy to handle powders from soluble solid materials. However, most spray dryer designs are suitable for producing substance in amounts from grams and upward using a strategy of drying the particles by increasing the temperature for vaporizing the solvent. An alternative strategy is to remove the solvent from the drying particles by vapor absorption onto solid absorptive materials such as silica gel or activated carbon [1, 2].

The purpose of the current study was to explore the principle of spray drying by vapor removal to enable; (i) micronization of small amounts of a compound (<100mg) in high yields (ii) using a gentle process not affecting the biologic activity of delicate substrates.

Material and Methods

The presented spray dryer system was built on the principle to remove the solvent vapors before the produced solid particles were separated from the process stream. This was accomplished by using a low flow rate well into the laminar flow range through the system, combined with a solvent absorbing step before the particles were separated from the gas stream (Fig 1). The design is a 900 mm long drying column with a liquid spray streaming inside a perforated tube in counter-current contact with vapor-depleted air streaming on the outside of a vapor-permeable membrane covering the perforated tube [3]. A thin rice paper was used as a membrane to separate the air streams, but still allowing passage of diffusing vapor.

Vapor was removed from the drying air using an absorption column containing activated carbon and silica gel in tandem. The vapor-stripped drying air was then returned to the drying column in a closed loop.

Process control was achieved with a control program written in LabVIEW. Spray was produced with a downward acting AeronebPro mesh nebulizer working at <5% of its full output, or typically 20 µL/min.

There were four characteristic flow rates in the system with typical values for aqueous solutions indicated within brackets (Fig 1):

- **Q_F: Flow through the product filter, (2 L/min).**
- **Q_N: Dry air entering the system with the nebulizer spray generation at a flow rate of 1.5 L/min.**
- **Q_S: A sheath air flow of 0.5 L/min added to the drying air immediately downstream of the circulation fan. The purpose was to decrease powder deposition on the vapor permeable membrane.**
- **Q_D: The circulation fan maintains a drying air flow of 50 L/min transporting vapor from the drying column to the vapor absorption column.**

By measuring all flow rates and critical vapor concentrations, a total mass balance of the solvent vapors during drying was obtained.

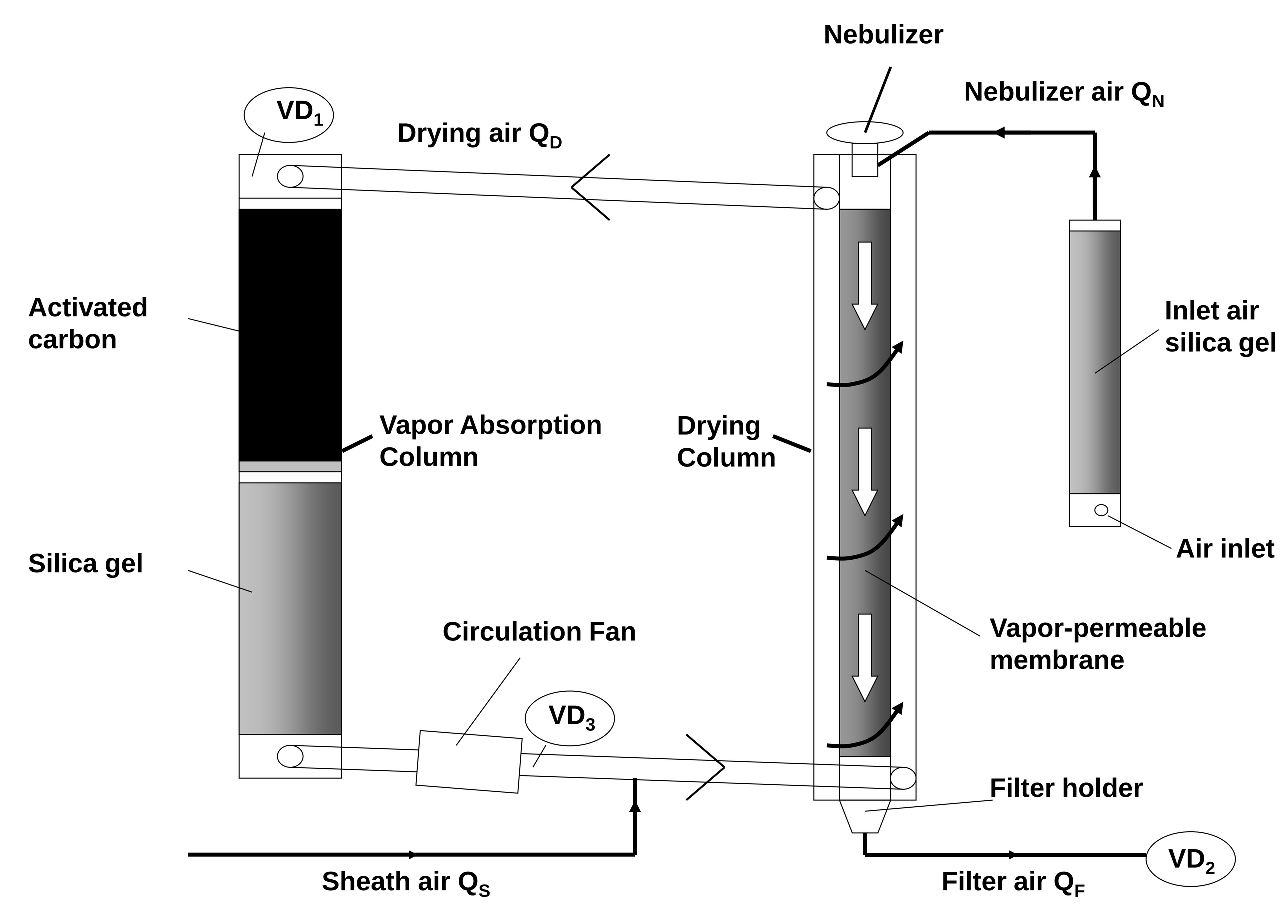
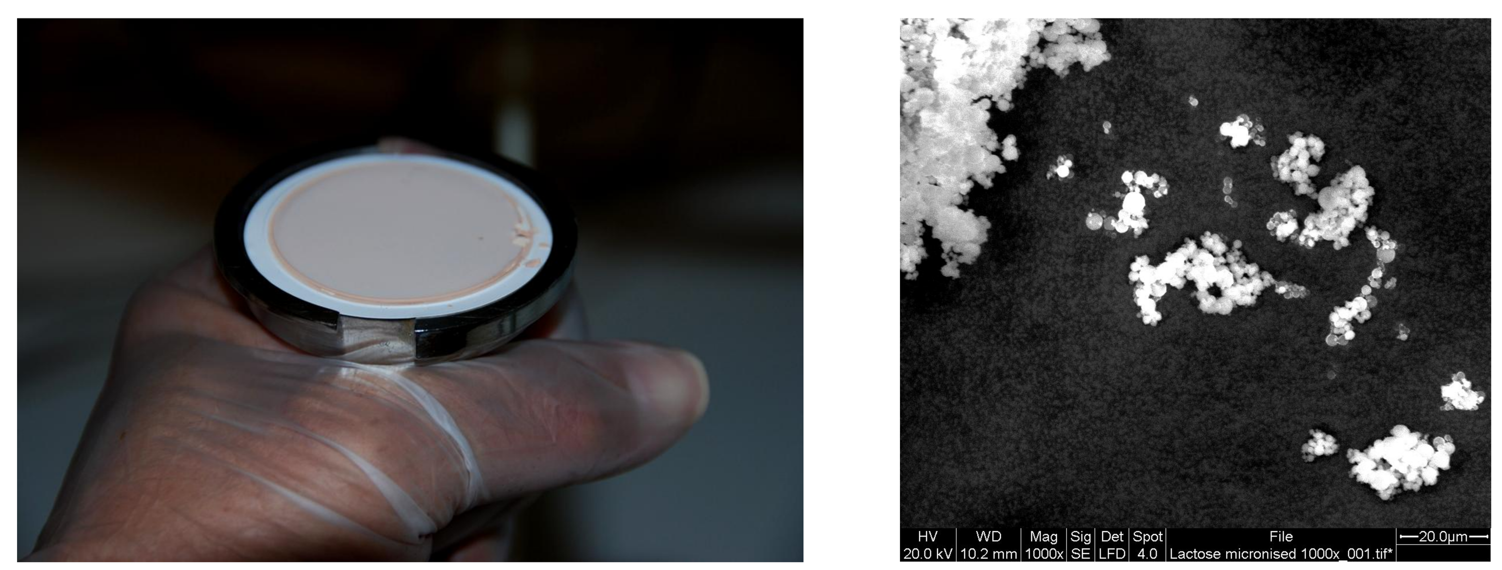


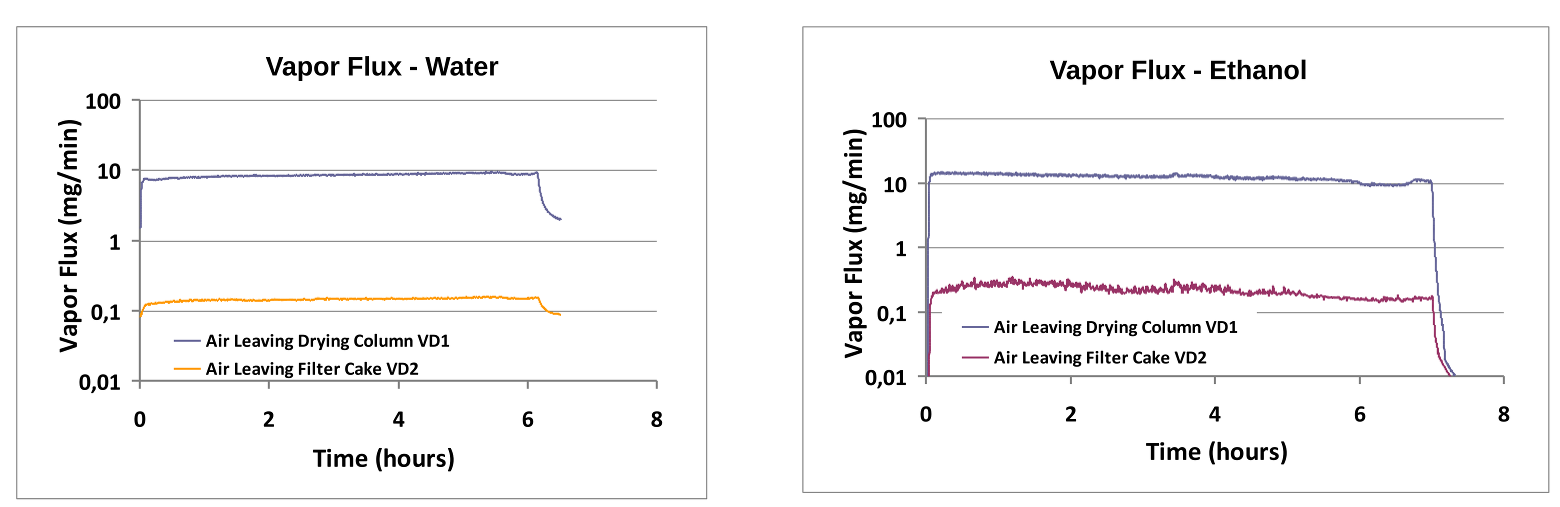
FIGURE 1: A scheme of the LaminarPace spray dryer. VD indicates the positions for the probes measuring vapor concentration/humidity in the system.



A) B)

Picture by Dr. Rod Forbes, University of Bradford, UK

FIGURE 2A: A filter cake of horse radish peroxidase on the 56 mm product filter.
B: Scanning electron micrograph of spray dried lactose powder in bulk.



A) B)

FIGURE 3: Vapor transfer in the drying column during continuous operation. The vapor flux transferred from the drying column to the absorption column is compared with the vapor flux passing through the product filter. A) Water B) 99.5% Ethanol

Results and Discussion

Countercurrent drying with process stream separation can be used for spray drying at room temperature. When the output from the Aeroneb nebulizer was kept below 5% of full output, vapor transfer of either water or ethanol from process stream to vapor absorption stream was nearly complete (Fig 3). Typically, more than 97% of either solvent added to the drying column was removed before the filter air exited the drying column.

A number of powders were successfully generated from both aqueous- and organic solutions. Typically, 20-100 mg substance were formulated as fine powders in yields >80% with sizes of the primary particles ranging from 1-10 µm. Fig 4 shows the particle size distribution of two aerosols generated from spray-dried powders. The laminar flow regime makes particle losses to the column interior easier to control. The sheath air system seems to be able to reduce substance losses in the drying column to below 10%. Most of the substance losses came from material retained in the emptied nebulizer (Table 1).

Spray drying at room temperature is a gentle formulation method. As a model for a biopharmaceutical, horse radish peroxidase spray dried from a 2.5% aqueous solution was shown to fully maintain its enzymatic activity [4].

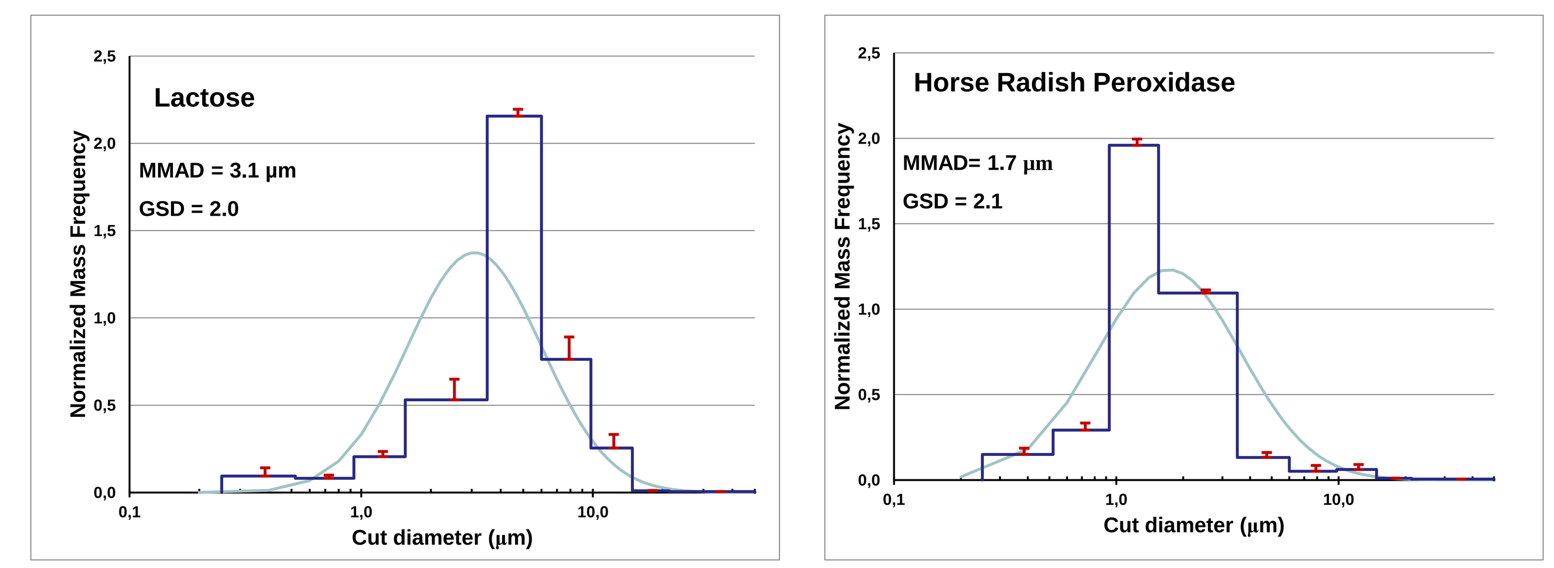


FIGURE 4: The particle size distribution of two spray dried powders aerosolized with the PreciseInhale system.

Substance	Lactose monohydrate	Horse Radish Peroxidase
Amount loaded	500 mg	103.87mg
Solvent	Water	5 mM PBS pH7.4
Volume	5 mL	4 mL
Concentration	10%	2.5%
Drying time	6 h	6h 30 min
Amount on filter	456 mg	102 mg
Recovery on filter	91%	95%

Table 1: Some important operational parameters and substance yield for lactose and horse radish peroxidase.

Conclusions

The LaminarPace spray dryer is a convenient method to generate small amounts of powder from precious substances in high yields. The collection of product on small filters considerably reduces loss of substance. Material retained on the filter can always be used either as a powder or redissolved and used in solution. The multiple options to control the operation of the LaminaPace hint at the potential for the technology to be used in particle design.

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3. Gerde, P., *System and Method for Producing Dry Formulations*, W.I.P. Organization, WO 2009/041900 A1.
4. Selg, E., et al., *Delivering Horseradish Peroxidase as a Respirable Powder to the Isolated, Perfused and Ventilated Lung of the Rat: The Pulmonary Disposition of an Inhaled Model Biopharmaceutical.* Journal of Aerosol Medicine and Pulmonary Drug Delivery, 2010. **23**(5): p. 273-84.