

# EFFECT OF CONCENTRATION, VIAL SIZE AND FILL DEPTH ON PRODUCT RESISTANCE OF SUCROSE SOLUTIONS DURING FREEZE DRYING

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## Introduction

In a freeze drying process, mass transfer and product temperature are dependent upon the resistance of the product matrix to water vapor flow ( $R_p$ ) [1].  $R_p$  is influenced by numerous factors such as nature of the product, solute concentration and freezing properties, and was found to differ between formulations and process conditions used. The objective of this study was to characterize product resistance as a function of dry layer thickness for various sucrose solutions using the SMART™ Freeze Dryer technology. SMART™ is a new PAT concept that employs Manometric Temperature Measurement (MTM) for the optimization of a lyophilization process during the first laboratory experiment. A pressure rise experiment is performed at user predefined intervals to determine the vapor pressure of ice at the sublimation interface ( $P_{ice}$ ) and the product resistance. Using steady state heat and mass transfer theory, product temperature at the sublimation interface ( $T_p$ ) and several additional derivative parameters are calculated. In addition, it is also possible to obtain temperature and resistance data for an entire batch during pre-existing freeze drying cycles, and to evaluate effects of material and process variations.

## Materials and Methods

### Materials

Sucrose was of analytical grade and used as received (Sigma-Aldrich, Germany). 5%, 10% and 20% (w/w) solutions were prepared with double distilled water. 5 mL (load: 203 vials,  $A_p = 3.46 \text{ cm}^2$  or 240 vials,  $A_p = 2.91 \text{ cm}^2$ ) and 20 mL (load: 91 vials,  $A_p = 6.33 \text{ cm}^2$ ) serum tubing vials were used during the experiments. All product vials were semi-stoppered with 20 mm Daikyo Flurotec stoppers (West, Germany) prior to the run.

### Experimental Setup

Freeze drying was performed using a FTS Lyostar II laboratory scale freeze dryer equipped with SMART™ Freeze Dryer technology (FTS Systems, NY, USA). An overview of the runs is given in Table 1. One row of empty vials was used to reduce radiation effects. Thermocouples (28-gauge) from Omega (Omega, Newport, CT, USA) were placed at the bottom center of product vials located in center and edge position.

Run #	% Solid	L <sub>ice</sub> (cm)	Vial Size (mL)
1	5	0,5	5 (3.46 cm <sup>2</sup> )
2	5	0,5	5 (2.91 cm <sup>2</sup> )
3	5	0,5	20
4	5	1,0	5 (3.46 cm <sup>2</sup> )
5	5	1,0	20
6	5	2,0	20
7	10	0,5	20
8	10	2,0	5 (3.46 cm <sup>2</sup> )
9	20	0,5	5 (3.46 cm <sup>2</sup> )
10	20	1,0	20
11	20	2,0	5 (3.46 cm <sup>2</sup> )

Table 1: Design of freeze-drying runs

### Freeze Drying Cycle

*Freezing:* 1°C/min to -40°C, hold for 180 min; *Primary (1°) drying:* 1°C/min to -25°C, chamber pressure 100 mTorr *Secondary drying:* optional; 0.2°C/min to 40°C, hold for 4h, end at +15°C.

### Manometric Temperature Measurement (MTM)

MTM measurements were performed in 60 min intervals during 1° drying, pressure data were collected at a rate of 10 points/sec. MTM analysis was performed by the SMART™ Freeze Dryer software. All equations concerning mass and heat transfer were already reported in the literature [2].

### Scanning Electron Microscopy

Cake morphology was examined using an Amray 1810 T Scanning Electron Microscope at 20 kV.

## **Results and Discussion**

The process data of a representative run for 5% sucrose is shown in Fig. 1. MTM product temperature data are in good agreement with TC measurements, indicating reliable derivative MTM results. Product resistance data was plotted against dry layer thickness (L<sub>dry</sub>) at the time of the measurement and compared with regard to the container system, solute concentration and fill depth used.

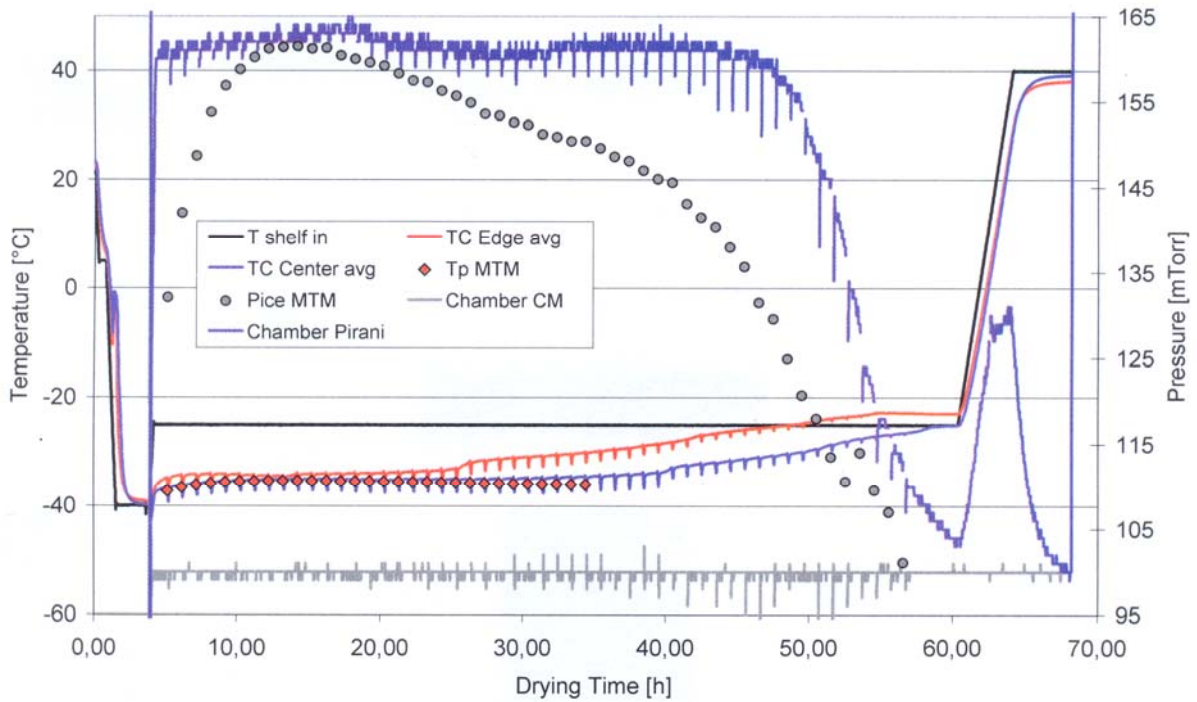


Fig. 1: Freeze-drying run, 5% sucrose.

There was excellent agreement of  $R_p$  data when using 20 mL vials and two types of 5 mL vials with different  $A_p$  (at identical concentrations and fill depth, cf. Fig. 2). The  $R_p$  curve showed an initial increase followed by a plateau phase. This type of resistance behaviour has been described for sucrose before. The results are accurate until about two thirds of primary drying and then become less reliable due to increasing batch heterogeneity.

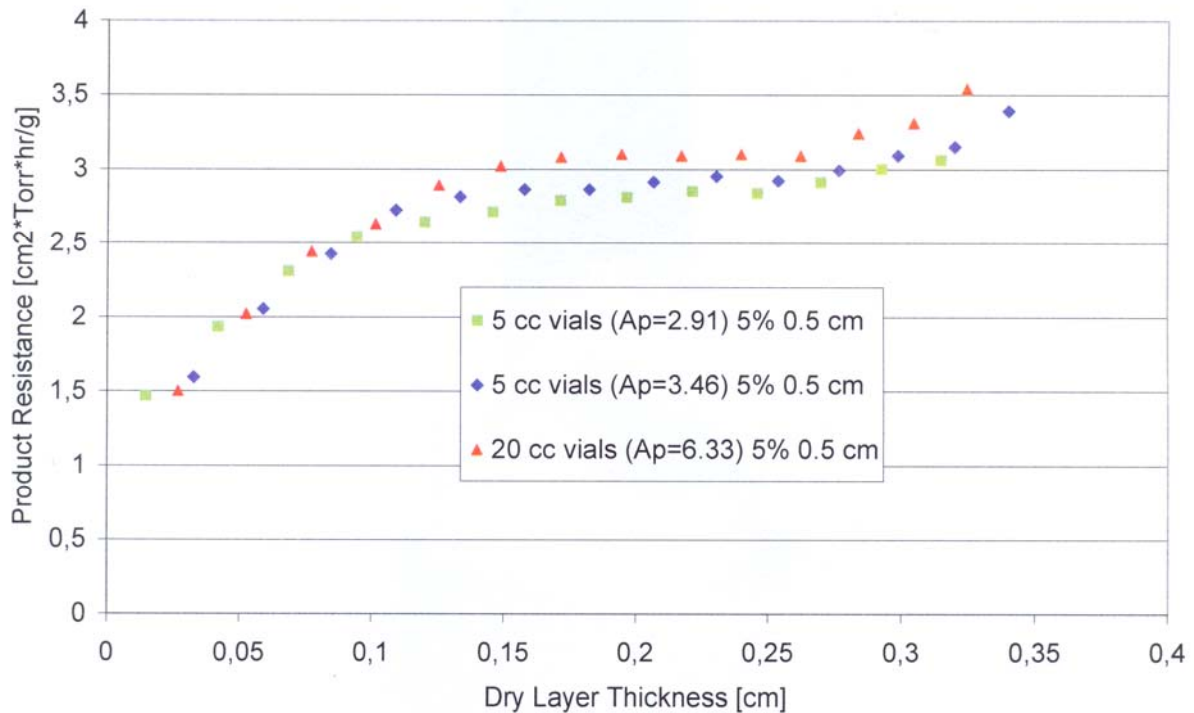


Fig. 2: Comparison of different vial types

As expected,  $R_p$  increased substantially at higher sucrose concentrations (Fig. 3). The resistance was comparable for 0.5 cm and 1 cm fill depth for 5% and 20%. However, at high fill depth (2 cm initial  $L_{ice}$ ) there was a systematic reduction in  $R_p$ . This reduction was either permanent or observed for at least 10 hours of primary drying, leading to significant increases in mass flow rates during that time.

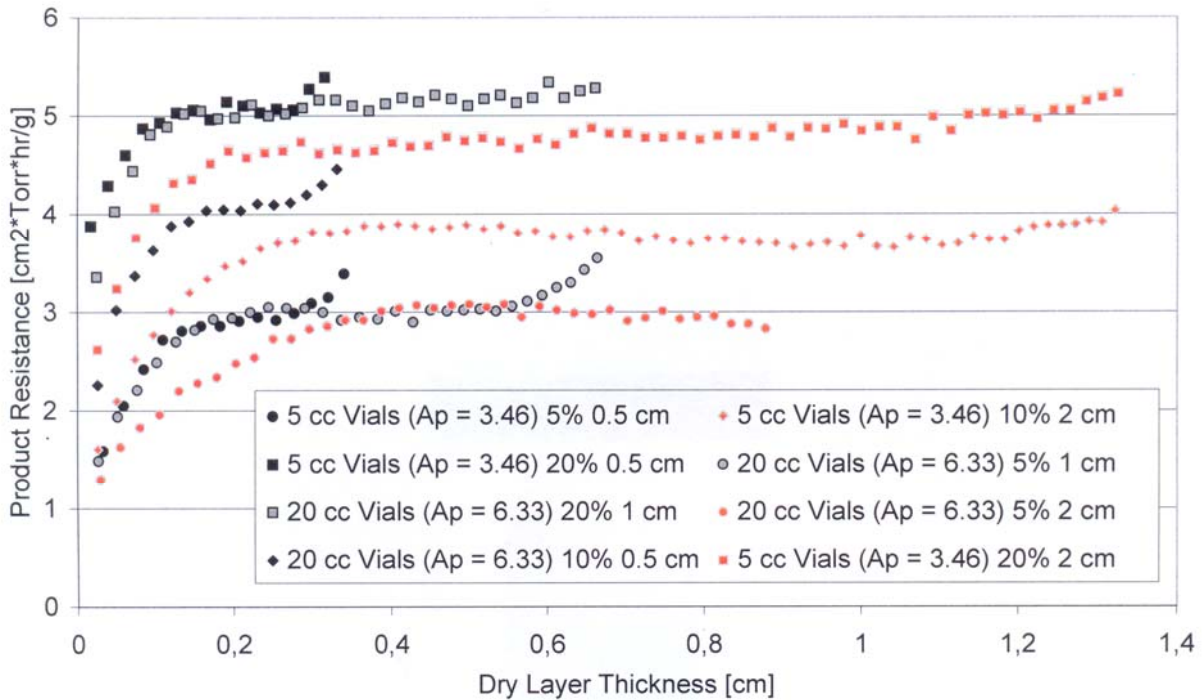


Fig. 3: Influence of Concentration and Fill Depth on Product Resistance

Further investigation of the influence of fill depth revealed a change in freezing behaviour for the 2 cm solutions. Following nucleation, the freezing time is extended and the temperature elevated relative to the lower volumes for more than 30 minutes (Fig. 4). A possible explanation for this observation could be insufficient heat removal capacity of the shelf fluid for this particular load and delayed heat equilibration in the large ice layer, resulting in lower heat transfer for the large volume. This leads to slower growth of the ice nuclei and an extended period of “slush” material characteristics.

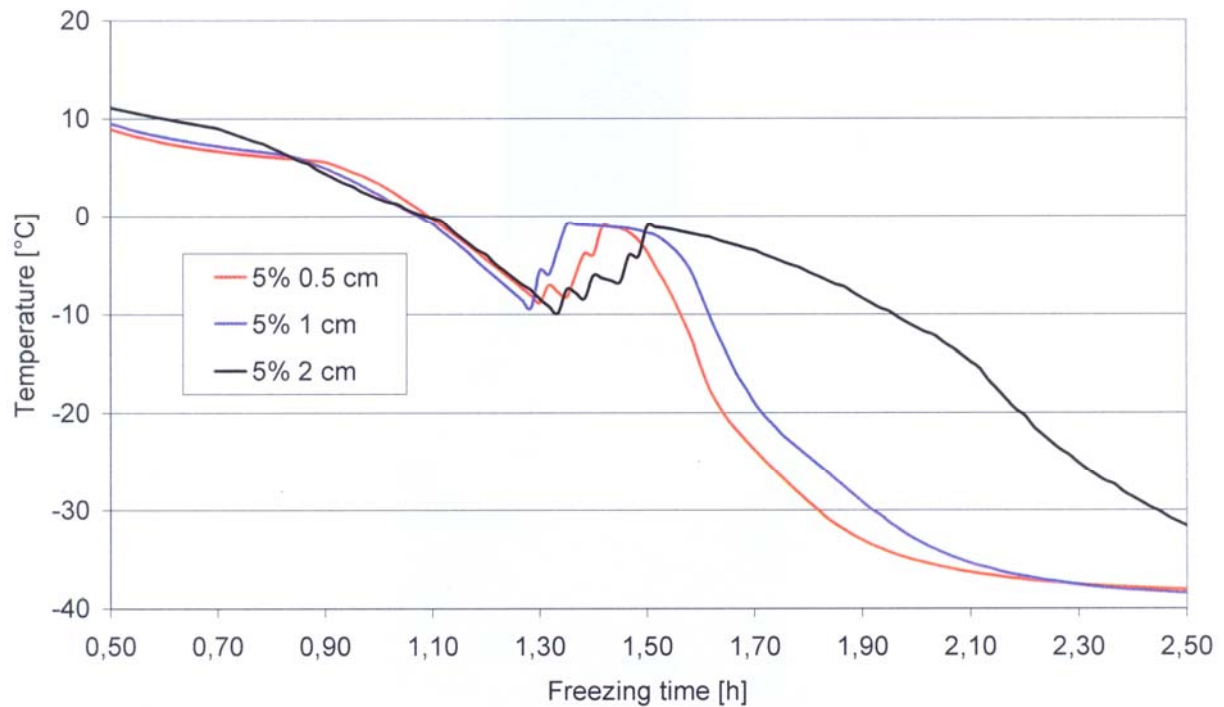


Fig. 4: Freezing behaviour at varying fill depths

This phenomenon would lead to an annealing-like effect during freezing resulting in larger ice crystals and pores in the cake, which could be shown using SEM (Fig. 5). The experiments performed with lower fill volume result in a cake morphology with smaller pores and therefore higher  $R_p$  values.

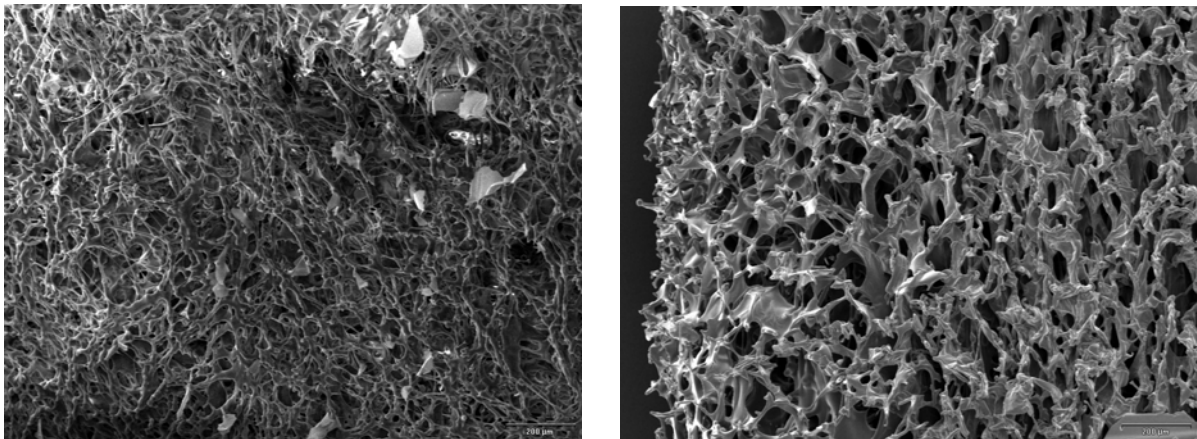


Fig. 5: SEM-Pictures of 5% sucrose with 0.5 cm (left) and 2 cm (right) initial ice thickness

## Conclusions

All 3 vial types investigated gave similar results in  $R_p$  over  $L_{dry}$  and therefore indicate the validity to directly compare runs performed with different sizes of serum tubing vials. As expected,  $R_p$  over dry layer thickness increased with higher solid contents. High fill volumes resulted in extended freezing and reduced product resistance or delayed increase of product resistance.

## References

1. Costantino H.R., Pikal M.J.: Lyophilization of biopharmaceuticals; AAPS Press, 2004
2. Tang X.C., Nail S., Pikal M.J.: Freeze-drying process design by manometric temperature measurement: design of a smart freeze-dryer; Pharm. Res. 22 (4), p. 685-700