Authors: MARGIT GIESELER, GILYOS GMBH
HENNING GIESELER, FREEZE DRYING FOCUS GROUP, UNIVERSITY OF ERLANGEN

INTRODUCTION

Freeze drying is known to be a time consuming process with primary drying phases ranging from several hours up to weeks, depending on the product. During primary drying the product temperature at the ice sublimation interface (T_p) must not exceed the critical formulation temperature (collapse or eutectic temperature, respectively) to prevent impairment of final product quality by collapse or meltback. T_p is determined by several factors like chamber pressure, shelf temperature, vial heat transfer coefficient and resistance of the dried layer.[1]

Product resistance (R_p) has been recently suggested as a critical product parameter (CPtP) in freeze drying because it instantaneously draws a picture of the (already dried) inner cake morphology at the point of measurement.[2] From a physical point of view, R_p of the dried product layer impacts the resistance to water vapor flow and thus indirectly determines the maximally allowable shelf temperature and primary drying time. With higher product resistance the product temperature increases and mass flow decreases.[1] Product resistance data allow the assessment of structural changes in the cake (e.g. microcollapse, shrinkage or collapse) as a function of temperature during primary drying. Moreover, product resistance data obtained during primary drying can reveal changes in the freezing situation of a batch (e.g. supercooling, nucleation) or can simply confirm consistency of the freezing behavior between batches during scale-up.[5]

Three methods for assessing dry layer resistance can be currently found in the literature: a high-vacuum microbalance technique, a single vial method [3] and Manometric Temperature Measurement (MTM) where the product resistance is derived from non-linear regression analysis of a MTM model equation.[4]

Early investigations classified the product resistance behavior into four categories (Figure 1).

Type 1 is the expected behavior for all formulations and types of materials where R_p increases almost linearly with the developing dry layer thickness of the product. In practice, this behavior can only be observed with crystalline materials since they do not undergo structural changes during primary drying. Type 2 indicates a high R_p value at the beginning of primary drying which can be attributed to the formation of a dense amorphous skin that prevents water vapor removal during this phase. After cracking of the skin layer, R_p increases linearly, similarly to Type 1 behavior. Type 3 and 4 both indicate a linear behavior in the early phase of primary drying, but the course of the data tends to form a curvature (or plateau) after a certain time. Such behavior is typically found for amorphous materials which undergo some microcollapse and / or shrinkage in the late phase of primary drying. Type 3 and 4 behavior may be distinguished by the slope of resistance increase.[3]

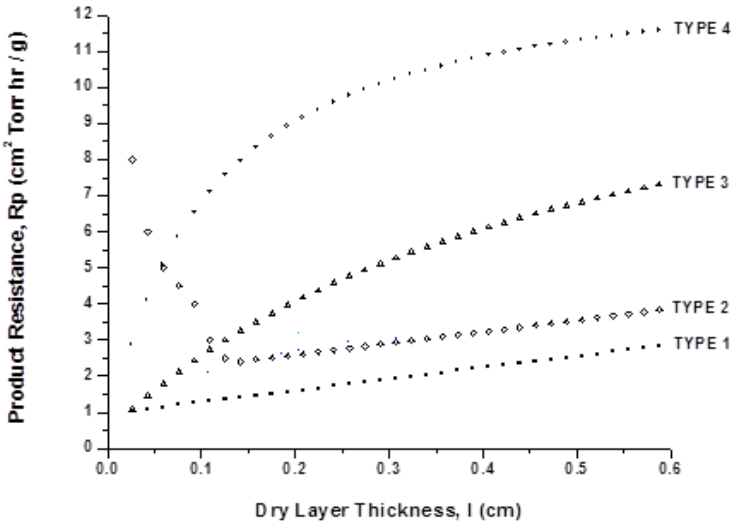

Figure 1: R_p behavior as proposed by Pikal [3]

This technical note summarizes results of trials investigating the product resistance of sucrose based on different experimental conditions and using the Auto-MTM feature of the SMART Freeze Dryer software.

MATERIAL AND METHODS

NF grade sucrose was obtained from Sigma and used as received. 5%, 10% and 20% (w/w) solutions were made by dissolving the respective amount of sucrose in USP grade water for injection. Prior to filling the solutions were filtered through a 0.22 µm filter (Millipore).
Primary packaging materials were 5 mL and 20 mL tubing vials from Wheaton with a 20 mm finish. Fill volumes were adjusted to give different levels of ice thickness. Table 1 provides a correlation of the ice thickness and corresponding fill volumes.

Table 1: Fill volumes of 5 and 20 mL vials required to obtain 0.5, 1.0 and 2.0 cm ice thickness (L_{ice}).

Container	Target L_{ice}	Required Fill Volume (mL)
5 mL vial, 20mm finish	0.5 cm	1.60
	1.0 cm	3.20
	2.0 cm	6.35
20 mL vial, 20mm finish	0.5 cm	2.90
	1.0 cm	5.80
	2.0 cm	11.60

One tray of vials (hexagonal packing profile) was placed on the center shelf of a 3 shelf Lyostar® II freeze dryer equipped with SMART™ for each experiment. Empty (dummy) vials were used in the outer rows to shield the vials filled with product from radiation. Aluminum foil was attached to the inside of the acrylic chamber door for the same reason. The bottom of the tray was removed prior to freeze drying to ensure maximum heat transfer from the shelf.

The following cycles were run in Auto-MTM mode (data collection interval 60 min):

Step	Cycle w/o annealing				Cycle with annealing			
	T_s SP [°C]	Ramp/Hold	Time [min]	Pressure [mTorr]	T_s SP [°C]	Ramp/Hold	Time [min]	Pressure [mTorr]
Freezing	5	R	25	---	5	R	25	---
	5	H	20	---	5	H	20	---
	-40	R	45	---	-40	R	45	---
	-40	H	240	---	-40	H	240	---
	---	---	---	---	-15	R	25	---
	---	---	---	---	-15	H	240	---
	---	---	---	---	-40	H	240	---
Primary Drying	-25	R	15	100	-25	R	15	100
	-25	H	4800 (TBC)	100	-25	H	4800 (TBC)	100
Secondary Drying	40	R	130	100	40	R	130	100
	40	H	240	100	40	H	240	100
Backfill and Stoppering	40	---	---	$600*10^3$	40	---	---	$600*10^3$

RESULTS AND DISCUSSION

a) R_p behavior as a function of the fill volume

The correlation between fill depth and R_p is illustrated in Figure 2 for 5% sucrose and L_{ice} values of 0.5 and 1.0 cm (5 mL vials) and L_{ice} values of 0.5, 1.0 and 2.0 cm (20 mL vials), respectively.
For both vial dimensions, R_p data for ice thickness values of 0.5 and 1.0 cm show a similar steep increase in the early phase of primary drying, followed by a formation of a plateau phase with progressing drying time. Note that the steep increase in R_p data at the end is a function of deviations in the MTM data fit.
The resistance values for the larger fill volume (L_{ice} = 2.0), however, reveal a different behavior. Here, the profile complies rather with the Type 3 curve than with Type 4. Apparently, the fill depth impacts the freezing situation of the solution, resulting in a different ice crystal size and hence in a different product resistance.

Figure 2: Product resistance in correlation to dry layer thickness

b) Dependence of R_p on solute concentration

Figure 3 depicts the relation between concentration of the solution and R_p. As expected, product resistance increases with higher concentration of dissolved solids. The increase in concentration from 5% to 10% resulted in a R_p value of 4 cm^2*Torr*hr/g, the step from 5% to 20% in 5 cm^2*Torr*hr/g. Despite of different fill volumes and different vial sizes, the R_p values of the 5% solution are comparable in the linear regions of the profiles. Therefore it may be assumed that for sucrose an increase in solute concentration of 5% results in an increase in product resistance of about 1 cm^2*Torr*hr/g.

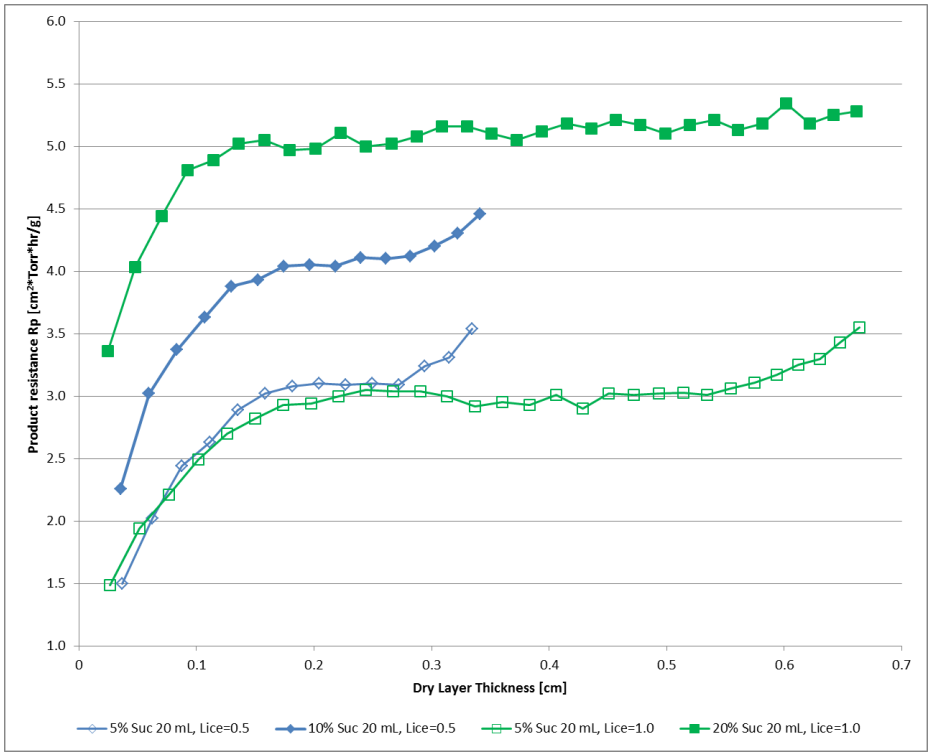

Figure 3: Product resistance based on solute concentration

c) Impact of Annealing

Annealing is often used to induce crystallization of excipients to prevent vial breakage, and / or to enhance ice crystal growth to reduce primary drying times and receive a more uniform pore size distribution. Figure 4 clearly pinpoints the benefit of an annealing step during the thermal treatment phase as illustrated by the product resistance profile. In the case of sucrose only ice crystal growth took place as the disaccharide remains amorphous.

During the freezing step, the formation of very small ice crystals is more pronounced with higher supercooling of the solution. Small ice crystal sizes in the cake result in the formation of small pores in the cake inner morphology which, in turn, increase the resistance to water vapor flow (high R_p). A different approach to avoid this situation is to control the nucleation, meaning to prevent a high super-cooling. Here, a few techniques to manipulate the nucleation temperature have been proposed in the literature.[5, 6] However, the most advanced concept is ControLyo™ – Nucleation on Demand technology. For further information about this new innovation, the reader is referred to specific literature which is available on the SP Scientific website.

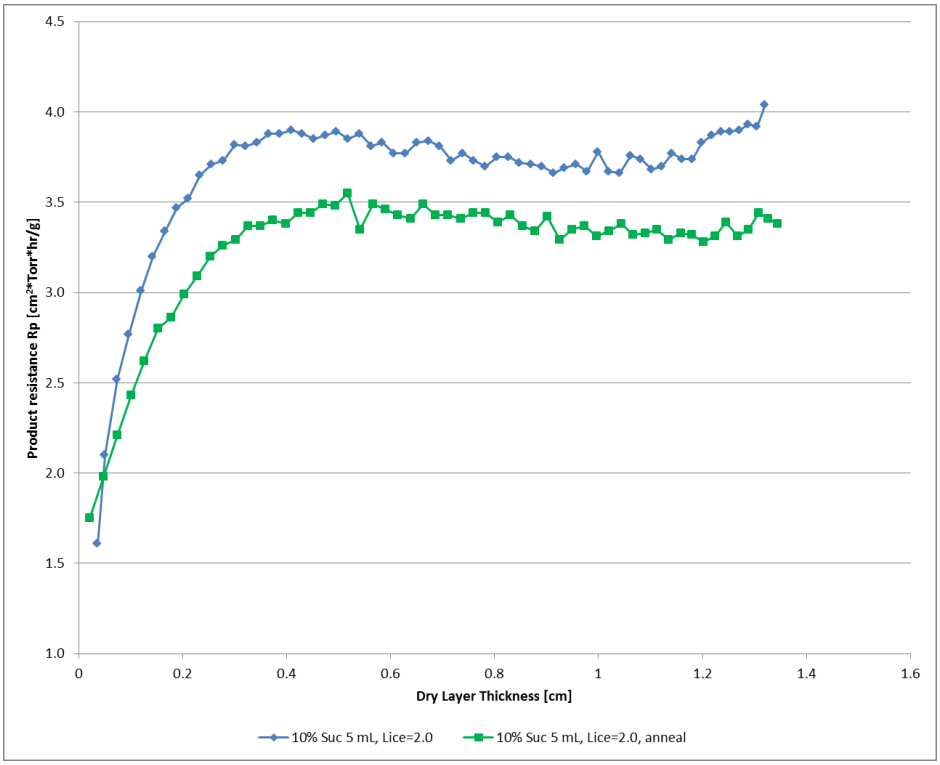

Figure 4: Impact of annealing on product resistance

SUMMARY AND CONCLUSION

The resistance of the product to vapor flow during primary drying has been accepted as a critical product parameter that impacts several process parameters. Lack of information about product performance during primary drying can lead to suboptimal product quality and/or problems during scale-up. The use of MTM allows an easy and reliable assessment of product resistance data. In this Tech Brief the impact of different solute concentrations, fill volumes and processing conditions on R_p were investigated and discussed for sucrose. With increasing solute concentration and fill volume, R_p increases. Adding an annealing step to the thermal treatment phase results in a decrease of R_p, promoted by larger ice crystals in the frozen layer.

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