Factors that influence product resistance and methods to measure product resistance

by **Dr Robin Bogner**
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Dr Robin Bogner
University of Connecticut, USA

Product resistance (R_p) is the resistance to vapor flow through the dried layer out of the vial during primary drying. Along with the vial heat transfer coefficient (Kv), product resistance is a key determinant of the product temperature. It can provide instantaneous structural information about cake morphology at the point of measurement. However, characterizing Rp remains the weakest part of any predictive model of primary drying.

Recently, Dr Robin Bogner from the University of Connecticut, USA presented a webinar that discussed the factors that influence product resistance and ways to measure it during primary drying of the lyophilization cycle for products in vials. This tech note summarizes the webinar and includes a selection of questions from the Q&A session.

Dry product resistance (R_p)

The R_p is important because it influences the product temperature profile which needs to be in an optimal range to avoid collapse, maintain stability of products and the time to complete primary drying. If the dry product is homogeneous, the R_p will increase with time and thickness of product layer (L_{dry}) equally. However, the relationship between R_p and L_{dry} can often be non-linear due to product heterogeneity, shrinkage around sides of vial or product microcollapse.

Traditionally, this association is expressed as an empirical equation, $R_p = R_0 + (A_1 * L_{dry}/(1 + A_2 * L_{dry}))$ with a constant (R_o) and refers to resistance at $L_{dry} = 0$ and two coefficients (A_1 and A_2).

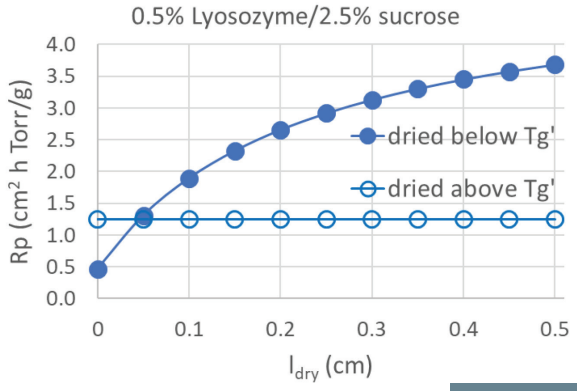
Factors that influence Rp

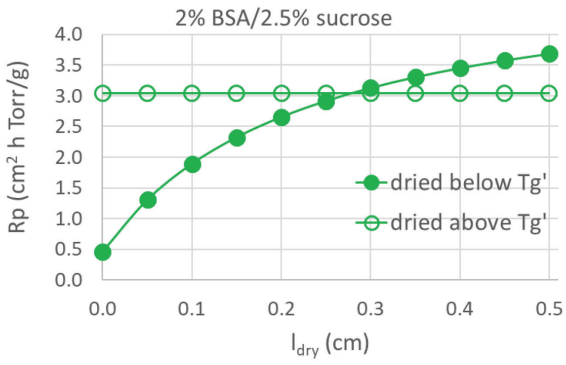
As R_p is so critical to lyophilization, it is worth considering the factors that influence this resistance and how these can be manipulated to optimize the freeze-drying process for a given product.

Formulation

Materials have, by nature, different resistances and, therefore, each product formulation may have different dry

Factors Influencing R_p versus L_{dry} : Microcollapse





	<Rp> (cm2•h•Torr/g)	
	Dried below Tg'	Dried above Tg'
0.5% Lysozyme/2.5% Sucrose	2.61	1.25
2% BSA/2.5% Sucrose	5.62	3.04

From values in Shivkumar (2019) based on data in Lewis (2010)

Tg' = glass transition temperature of the maximal freeze concentrate

Figure 1. Microcollapse above the Tg' lowers the dry layer resistance

product resistance during freeze drying. These differences act as a physical barrier for vapor flow through the dried layer and slow the sublimation process.

Recent work can be misinterpreted to suggest that only concentration and formulation influences R_p (Shivkumar *et al* 2019 and Pikal *et al*, 2018) but there is also evidence that the freezing protocol, as well as product microcollapse created with different shelf temperatures approaching the glass temperature of a formulation (T_g') can affect the Rp value (Lewis *et al*, 2010) (Figure 1).

Ice nucleation temperature

Studies have shown that higher ice nucleation temperature (lower degree of supercooling) and high freezing rates lead to lower resistance irrespective of whether the nucleation is controlled or not (Searles *et al*, 2001).

Annealing

Annealing is often used in freeze-drying to induce crystallization by holding a product at a predetermined temperature for a specified duration. This can increase ice crystal sizes with more pores on the cake, which can decrease the primary drying time. Studies were described in the webinar that demonstrate an increase in primary drying rate that reduces the R_p when above T_g', but not below T_g' (Searles *et a*l, 2001).

Rate of freezing

When comparing fast (ice nucleation at -10°C and cool at 5°C/ min) and slow (ice nucleation at -5°C and cool at 0.2°C/ min) freezing of an amorphous formulation of 100 mg/mL protein, it is evident that the smaller pores that are produced during faster freezing lead to higher R_p values.

Other factors that may influence R_p values include vial dimensions, which influence the freezing rate and pattern, and phase transitions during the freezing and drying cycles, all of which are formulation dependent.

Ideally, the R_p should be measured using the same formulation, vial, fill, freezing and primary drying protocols as expected for the target cycle.

Methods to measure Rp

To measure the value of R_p, several methods can be applied which take into consideration whether the product is in a batch or a single vial and if it is in real time or time-averaged with controlled or uncontrolled nucleation. Each of these scenarios were discussed in the webinar but for this technical note, we will outline how R_p can be measured for a batch of samples.

Manometric temperature measurement (MTM) is one of the most common methods of measuring R_p using the pressure rise within the chamber. An isolation valve between the two chambers is closed very quickly and the rise in pressure can be measured over about 25 secs. With this information, the R_p value can be calculated from a complex equation that considers various other parameters including L_{dry}. Some systems may have a SMART MTM that produces a spreadsheet of all the appropriate data as soon as the measurement is made to plot the Rp and L_{dry}.

Without MTM, the batch average real-time sublimation rate can be calculated from Tunable Diode Laser Absorption Spectroscopy (TDLAS) or a heat flux sensor.

For a single vial, if either TDLAS or heat flux data is not available to measure sublimation rate, one can determine the sublimation rate using average temperature, overall drying and heat transfer coefficient. Determine the sublimation rate for each vial using the temperature of each thermocouple and the known Kv for each vial.

It is, therefore, possible to calculate R_p for many different systems with various data that you have available.

Summary

The freezing protocol has a significant influence on the structure of the dried cake and R_p. There are several factors e.g. formulation, annealing, microcollapse and phase transitions that influence the value of R_p and these should be considered when optimizing a lyophilization cycle for a specific formulation.

Measuring R_p is possible in different ways according to the available data and technology. Batch average R_p and L_{dry} can be measured using MTM, TDLAS and heat flux, but even in the absence of these advanced technology, cycle data (product temperature, K_v and time) can be used to provide batch or single vial R_p and L_{dry} values.

To view the full webinar and download the slides, please go to the archived webinars on our website https://www.spscientific.com/Webinars/Archives/.

References

Shivkumar G, Kazarin PS, Strongrich AD, Alexeenko AA. AAPS PharmSciTech. 2019 Nov 1;20(8):328.
Lewis LM, Johnson RE, Oldroyd ME, Ahmed SS, Joseph L, Saracovan I, Sinha S. Aaps Pharmscitech. 2010 Dec 1;11(4):1580-90.
Searles JA, Carpenter JF, Randolph TW. Journal of pharmaceutical sciences. 2001 Jul;90(7):872-87.)

Q&A Session

Selected questions from the Q&A Session

1. **In regards to nucleation temperature as one of the factors that influence R_p, when you have a high fill volume, you don't have a complete ice plug, would there be differences in R_p on top vs the layer in the bottom?**

   Particularly when the fill volume is high, there can be heterogeneous distribution of ice versus solute. If the solute is more concentrated toward upper quarter of the cake, most of the resistance will be associated with that upper layer; once that upper layer has undergone sublimation, it provides a relatively constant R_p. However, if the question is about formation of a "skin" of amorphous solute on top of the "frozen plug", which contains a lower solute concentration, the R_p vs. L_{dry} profile can be very strange. In his 1985 paper on using lab data to design a freeze-drying process, Mike Pikal labelled this Type II behavior (Pikal MJ. PDA J.Pharma. Sci. Tech. 1985 May 1;39(3):115-39).

2. **What is the impact on the R_p of an increased vial diameter (same total volume of vial and drug product solution)?**

   A smaller vial with a high fill, freezes more slowly than the same volume in a larger vial. Since the freezing rate and pattern influence R_p, particularly for amorphous formulations, the larger vial would be expected to result in faster freezing, with potentially higher R_p at any given Ldry. However, I would expect this effect only with very large differences in vial sizes. Furthermore, toward the end of primary drying the product in the smaller vial, there would be a thicker dried (or nearly dried) product layer over the sublimation surface, providing a higher R_p toward the end of the cycle.

3. **How much of an influence does the primary drying pressure have on R_p?**

   Theoretically, there are two considerations: First, at high enough sublimation rate in a weak cake (i.e., low concentration and/or partially crystalline solids) the vapor flow can alter the cake structure, sometimes even blowing some of the solids out of the vial. In that case, the R_p would be reduced. The second consideration assumes no change in pore structure. At 100 mTorr, the mean free path of water vapor is about 500 microns, which is larger than the pore size in most lyophilized cakes. At these conditions, the resistance is independent of pressure. However, the resistance to flow through the vents in the stopper can decrease with increasing pressure since those vents are larger than 500 microns. This may seem counterintuitive, but recall that the resistance is defined in terms of mass flow, not volume flow; as the pressure increases, the mass/volume also increases.

6. **With respect to the ratio of height/diameter you mentioned that will influence R_p, do changes in vial sizes change the R_p constants also? Do you need to repeat R_p determination?**

   R_p depends on the formulation, concentration, and freezing rate (including the ice nucleation temperature). Since the vial size and fill volume can influence the way the product freezes, in an ideal world you would determine R_p in the vial at a fill depth and freezing protocol expected. I repeat R_p determinations, since the distribution in ice nucleation temperatures is random, if not controlled.