



LYO CALCULATOR

User manual

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2015

Table of contents

Introduction.....	2
Background.....	3
Methods.....	4
Procedure.....	6
Useful data.....	8

Introduction

Lyo Calculator is a tool with a Graphical User Interface (GUI) for computation of a preliminary drying stage during lyophilization (freeze-drying) in a pharmaceutical vial. The program allows the user to calculate useful properties of a dried product and sublimated vapor during drying.

Lyo Calculator is available at Pharmahub.org (<https://pharmahub.org/resources/lyocalculator>) and open for all users.

Background

Freeze-drying (lyophilization) is a process in which the product is sublimated for better storage and transportation. Freeze-drying consists of several steps:

1. Freezing of the solution. The solution temperature after freezing is around $-40\text{ }^{\circ}\text{C}$.
2. Primary drying. This step is the longest and most expensive one. Chamber pressure is dropped to almost vacuum conditions, and the shelf temperature is slightly increased, so sublimation process runs. During sublimation, dried product (cake) appears on top of the solution and approaches the bottom of the vial. The process is shown in figure 1. Lyo Calculator computes properties at this stage.
3. Secondary drying. After all ice is sublimated, some moisture may still remain in the drying product. To remove it, secondary drying is applied. Shelf temperature is elevated and maintained at a temperature between 20°C and $40\text{ }^{\circ}\text{C}$ for several hours

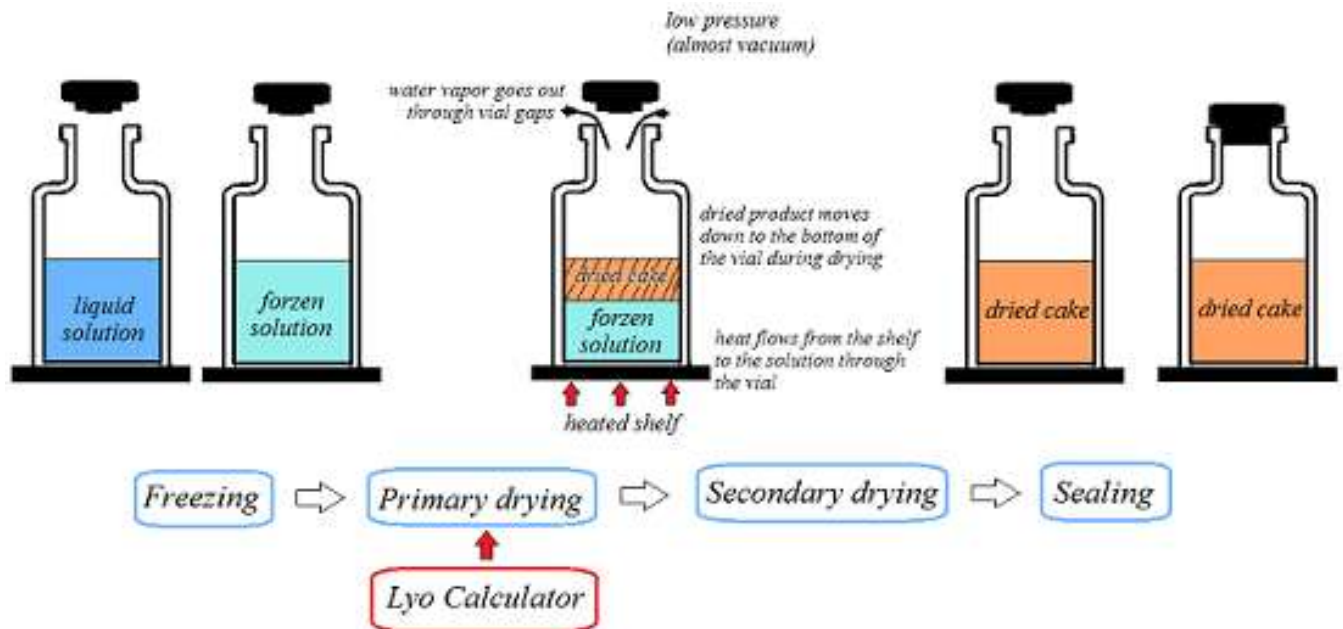


Figure 1. Primary drying process

Methods

The Lyo calculator uses pseudo steady- state heat and mass transfer model to compute vapor pressure, product temperature, sublimation rate, and dried product thickness. The steady- state model can be used because of the following reasons. First of all, the volume flow rate to system volume ratio is large, so step changes in chamber pressure changes pressure of other parts almost instantaneously. Moreover, step change of shelf temperature causes unsteady behavior of the process only for 15-30 minutes, so the time dependence is relatively small comparing to the drying time which is usually more than 24 hours. So shelf temperature T_s and chamber pressure P_{ch} are constant throughout the primary drying.

Generally, many factors are included in total resistance. The current model uses only the vial resistance expression

To solve the problem, the initial solution length is found first:

$$l_m = \frac{V}{\rho_i A_p} (1 - c(\rho_w - \rho_i))$$

Where V is a fill volume, c is solid concentration, A_p is the product cross-sectional area, ρ_i is the density of ice, and ρ_w is density of water.

Then, the initial length and water volume is divided into ten equal regions:

$$l = \frac{nl_m}{10}$$

And

$$dm = (1 - c) * \frac{V}{10}$$

Where n is an integer ranging from 0 to 10.

The initial sublimation temperature is set to be the shelf temperature.

After that, each station, sublimation temperature, vapor pressure, sublimation rate, drying time, and the ratio of dried product are found:

1. The product resistance is obtained by

$$R = R_0 + \frac{a_1 l}{1 + a_2 l}$$

Where a_1 and a_2 are constants obtained, and R_0 is initial resistance. These coefficients are obtained from experimental data (see Useful data section)

2. The vapor pressure of ice is found as

$$P_0 = 2.6983 * 10e^{\left(-\frac{6144.96}{T}\right)}$$

Where T is sublimation temperature at each time step. At the first step, the sublimation temperature is equal to the shelf temperature T_s .

3. Change in sublimation temperature is found as

$$\Delta T = \frac{24.7(l_m - l)(P_0 - P_c)}{R} - \frac{0.0102(l_m - l)(T_s - T)}{1 - 0.0102(l_m - l)}$$

4. New sublimation temperature T is found using an equation

$$P_0 - P_c - \frac{A_p K_v R_p (T_s - T - \Delta T)}{A_p 1833} = 0;$$

5. Sublimation rate is found as

$$\frac{dm}{dt} = \frac{A_p (P_0 - P_c)}{R}$$

6. The product temperature becomes a sum of the sublimation temperature and a change of it and a specific step

7. Drying time at each step is found as

$$t_n = \frac{dm}{dm/dt}$$

8. The percent dried can be found as

$$\frac{l}{l_{max}} * 100\%$$

Steps 1 to 8 are continued until $n \leq 10$.

The total drying time is a sum of all drying times at each interval

$$t_{total} = \sum_{n=0}^{10} t_n$$

Procedure

To get data from Lyo Calculator, do following steps:

1. Go to <https://pharmahub.org/resources/lyocalculator> and launch the tool
2. Input required variables in folders “Vial/solution properties” and “Chamber/Resistances”
 - 2.1. Input Area of a product, Area of the vial, fill volume, the heat transfer coefficient, and go to the next step. Note: some vial geometries are involved in the solver.
 - 2.2. Input resistance coefficients, solid concentration, and process parameters. Note: preset resistance coefficients for some solutions can be used.

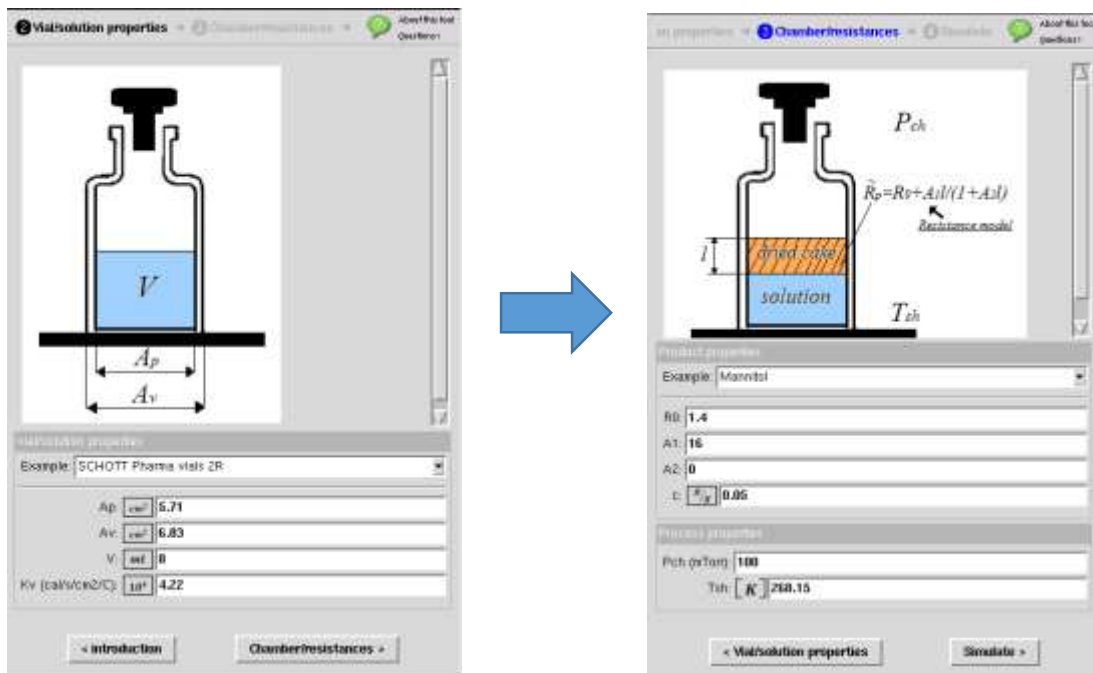


Figure 2. Input procedure (Mannitol 5%, W5816 vial type)

3. Click “Simulate” button and get solution
4. Results will be presented as a set of graphs. Calculated values are product temperature, vapor pressure, sublimation rate, and percent of the dried product.

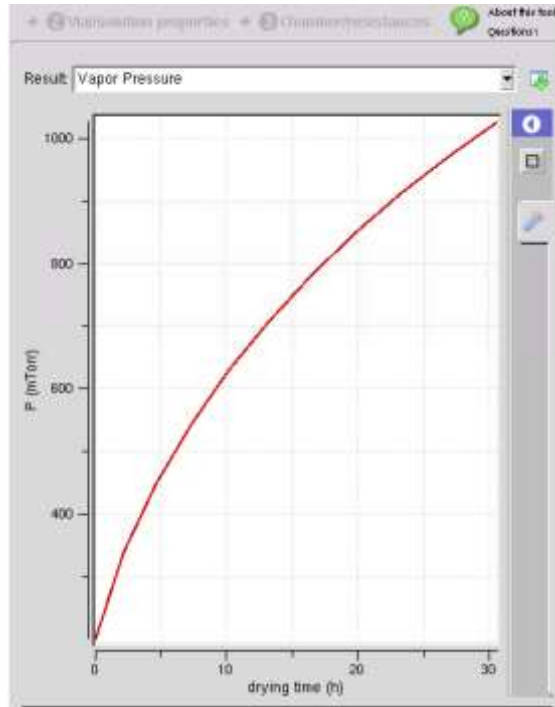
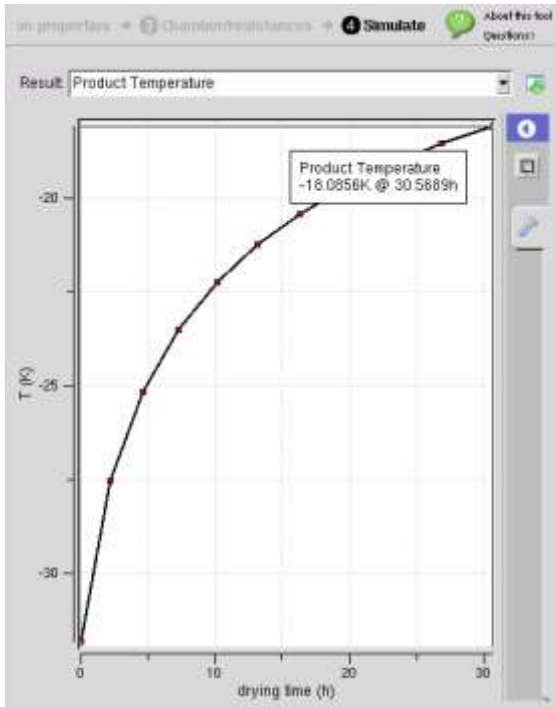


Figure 3. Product temperature and vapor pressure as functions of drying time

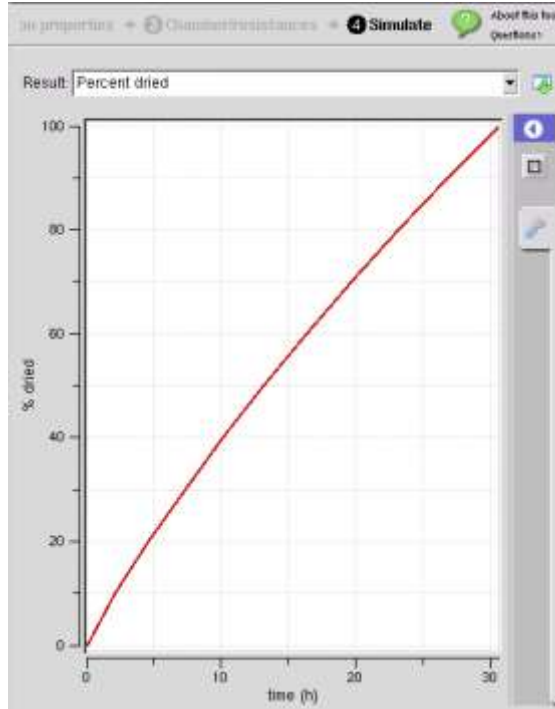
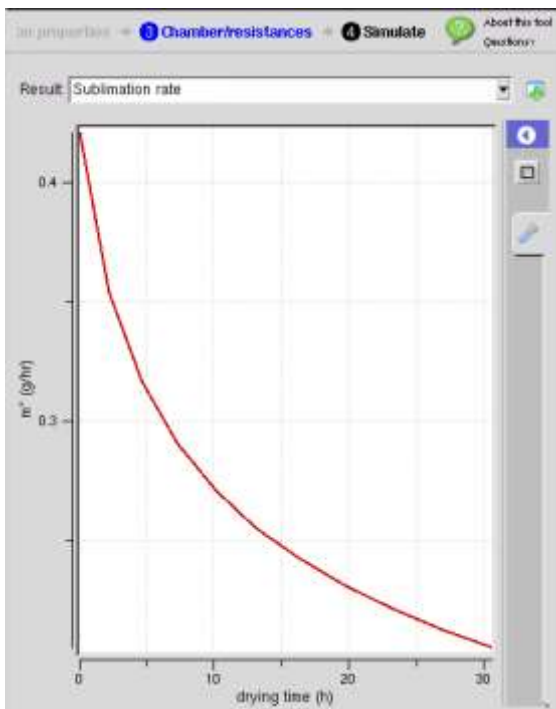


Figure 4. Sublimation rate and percent dried as functions of drying time

Useful data

Product resistance constants for different solutions:

Product type	R0	A1	A2
Aqueus	1	10	1
BSA/Sucrose	1	10	2.5
Sucrose	0.2	26	1.5
Mannitol	1.4	16	0
Povidone	1.13	5	0

Dimensions of vials for different fill volumes:

SCHOTT Pharmaceutica Vials					
Type	Fill Volume (ml)	diameter vial(cm)	diameter product(cm)	Area vial (cm ²)	Area product (cm ²)
2r	4	1.6	1.54	2.01	1.86
4r	6	1.6	1.54	2.01	1.86
6r	10	2.2	2.13	3.80	3.56
8r	11.5	2.2	2.13	3.80	3.56
10r	13.5	2.4	2.33	4.52	4.26
15r	19	2.4	2.33	4.52	4.26
20r	26	3	2.93	7.07	6.74
25r	32.5	3	2.93	7.07	6.74
30r	37.5	3	2.93	7.07	6.74

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