How Lowering the Pressure may Improve the Freeze-Drying Recipes and Accelerate the Lyophilization Cycles for Compounds with Low Critical Temperatures. New Biotechnological Active Ingredients.

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Abstract

New biotechnological pharmaceutical products are requiring low freeze-drying temperatures during the primary drying. Lowering the pressure thus is mandatory, but against the common knowledge, going to the minimum pressure possible can accelerate the lyophilization cycle. Freeze drying technology shall be updated to the new required process conditions, including improvements to enable effective regulation at low chamber pressures.

1. INTRODUCTION

Stability of the new biotechnological pharmaceuticals

The new biotechnological pharmaceuticals have a challenging stability (preservation) and cryopreservation is being the current usual solution. Nevertheless, freezing and specially thawing can be endangering for the molecules. Additionally, preserving the cold chain during the logistics and distribution, is a challenge and barely impossible at some regions of the globe.

Freeze drying can be an alternative for the preservation at room temperature of these valuable and sensitive new pharmaceutical products.

After years of development of the new biotechnological pharmaceuticals, now the focus starts also to be its stability, and thus, their viability for the freeze-drying process.

2. DISCUSSION

From a homogeneous liquid solution to a heterogeneous frozen solid

Most of the pharmaceuticals to be freeze dried, are highly diluted homogeneously in water, typical concentrations are above 90% water for less than 10% solid content.

At the first stage of freeze drying, the freezing step, pure ice crystals form and grow, concentrating and surrounding the remaining dissolution, that at the end also solidifies and ends to be a dense mesh uniformly present at the whole volume but segregated from the surrounding pure ice crystals.

The pure ice and the product mesh (what after the drying process will be the final solid content) are now a heterogenous frozen solid.

The thermodynamic behavior of this 90% pure ice solid, can be considered in accurate approximation to be as pure ice. This is the reason why the freeze-drying scientists are referring always to the pure ice sublimation data for the primary drying.

P (mbar)	Tv (ºC)
0.30	-32.44
0.10	-42.15
0.05	-47.91
0.03	-52.03
0.01	-60.54

Table 1: Sublimation temperatures (Tv) vs pressure for pure water ice

Pressure role in freeze drying

Pressure plays a key role during the primary drying of a freeze-drying process, when it is lowered below the triple point (6mbar) and stablishes the change-phase temperature (from ice to vapor) for the removal of all the pure ice (primary drying).

The drying temperature may never exceed the critical temperature of the concentrated solution (mesh), what is specific for each pharmaceutical compound.

The efforts of the freeze-drying scientists are focused in finding the proper package of excipients, that are neutral for the active ingredient, but helps the freeze-drying process to be viable. The excipients protect the pharmaceutical of thermal stress, low temperatures, ph swifts, among others. But also, and not less important by increasing the critical temperature of the compound.

Heat transfer and sublimation rate

All heat transfer processes require (or cause) a temperature gradient. Heat is naturally transferred from the hot source (high temperature) to the cold sink (low temperature), as an example during the primary drying:

- Shelves temperature: 10ºC
- Product temperature: -30ºC

Heat is transferred from the shelves to the product causing the sublimation (drying) process.

Shelves temperatures are controlled directly by the freeze dryer. The product temperature is indirectly set by the controlled pressure (also by the heat and mass transfer of the process, the water vapors removed).

For increasing the heat transfer and thus the sublimation rate (speed), the temperature difference may be increased. Shelves needs to be set at a higher temperature and/or the product temperature needs to be lowered by reducing the pressure.

But, decreasing the pressure has another important and crucial effect on the process, as lowering the pressure reduces the air/water vapor molecules between the shelves and the vials containing the product, lowering the heat transference. For the same temperature difference, shelves-product, a lower pressure causes less heat transference.

Lowering the pressure has two opposite effects on the heat transfer, increasing the temperature difference and/but lowering the transferred heat by worsening the transfer media.

For most of the applications increasing the pressure has led in better performance. But with the low critical temperatures, that we may encounter with the new biotechnological pharmaceuticals, this common knowledge rule of increasing the pressure for improving the process, may revert.

Heat transfer between shelves and vials:

$$\frac{dq}{dt} = A_v \cdot K_v \cdot (T_s - T_b);$$

Equation 1: Where dq/dt is the transferred heat in [W], Av the contact surface between vials and the shelves [m2], Kv the heat transfer coefficient [W/m2 ºC], Ts the shelves temperature [ºC] and Tb the product bottom temperature [ºC]

The Kv value and its dependance with the pressure

The heat transference coefficient has been precisely described and parametrized over the last decades **[1][2]**, it is composed by conduction (contact) between the vial and the shelves, convection, heat transferred through the air/water vapor contained between the shelves and the vials, and finally heat radiation.

It does not depend on the product, but on the container (vial) and shelves characteristics. It is highly dependent on the pressure, as lower the pressure, less air/water vapor is left between the vial and the shelf, and convection heat transfer reduced.

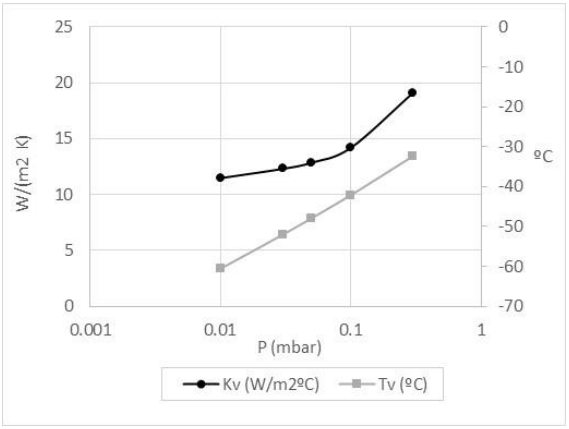

*Figure 1: Solid black circles: Kv values vs pressure for the ISO vial 6R, plot obtained using values from **[3]**. Solid grey squares: Sublimation temperature versus pressure, plot from table 1.*

For a quick evaluation of the heat transfer capacity (sublimation rate) at different pressures, equation 1 can be evaluated with Tv (sublimation temperature at chamber pressure) as Tb (temperature of the product at the bottom). This approximation is only accurate for very low product heights, below 1mm and at the beginning of the primary drying process.

P (mbar)	Kv (W/m2ºC)	Tv (ºC)	Ts (ºC)	Heat [W]	Sublimation rate capacity [kg/h]
0.30	19.12	-32.44	10	4057.264	5.12
0.03	12.34	-52.03	10	3827.251	4.83
0.30	19.12	-32.44	-30	233.264	0.29
0.03	12.34	-52.03	-30	1359.251	1.72

Table 2: Heat and sublimation rate capacity at four scenarios: Pressures of 0.3 and 0.03, shelves temperature 10ºC and -30ºC. Contact surface considered: 5m², sublimation enthalpy 3850J/g. Product height less than 1mm.

From table 2 the maximum sublimation rate occurs at the highest shelf temperature (10ºC) and highest pressure (0.3mbar).

At high shelf temperature (10ºC), reducing the pressure decreases the sublimation rate, while at the low shelf temperature (-30ºC) lowering the pressure increases the sublimation rate.

This phenomenon can be understood by evaluating the equation 1 and figure 1, and how decreasing the pressure affects Kv and Tb (Tv in our approximation).

When convection is almost zero (pressures close to 0.01mbar) the Kv value is barely affected by the pressure, while the sublimation temperature still linearly decreasing.

As lowest the temperature of the shelf, the closest to the sublimation temperatures, and more relevant are the effects of reducing the product temperature by reducing the pressure.

The critical temperature of the products constrains the maximum pressure and shelf temperature, and for its proper evaluation our approximation is only partial. It is required to introduce in the discussion the dried layer, the mesh left when the pure ice is removed. As explained earlier the concentrated product (mesh) at the frozen part does not play a substantial role, but when it is free of ice, it is a highly porous media that offers a resistance to the scape of the vapors, with a consequential pressure gradient and an important effect on the sublimation pressure and consequently the product temperature.

The dried layer, a complete model for the primary drying.

There is consensus among the freeze-drying scientists regarding the modelization of the primary drying for products in vials **[4]**. It is a good approximation to consider that the drying happens from the top of the product to the bottom with a horizontal plane (the sublimation front) dividing the frozen product from the already dried layer (DL), figure 2.

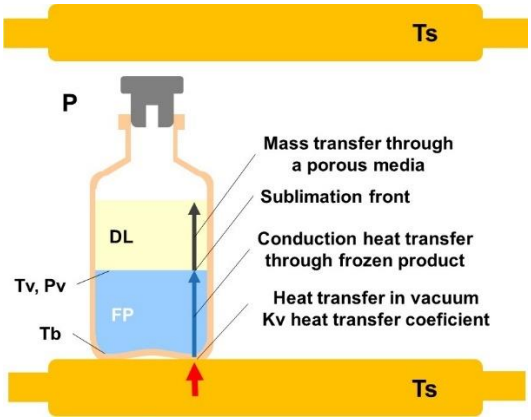

Figure 2: Schematic of the primary drying model

The heat transference at the frozen product (FP) is considered one dimensional conduction, being the temperature of the sublimation front (Tv), pure ice phase change at the pressure Pv. The difference between the controlled pressure of the freeze dryer P and Pv, depends on the characteristics, porosity of the dried layer, as well as its length, that increases during the drying.

The resistance of the dried layer to the vapors flow it has been studied and detailed at the literature [5]. As per the small size of the pores the flow is at molecular regime, depending only on the length of the layer but not depending on the pressure.

By the coupling of all the different parametrization described: Shelves-vial heat transfer, conduction at the frozen product and pressure expansion at the dried layer, it is possible to link the pressure of the chamber with the temperature of the shelves, to accurately calculate the product temperature at the sublimation front and the bottom vial, during the whole drying process.

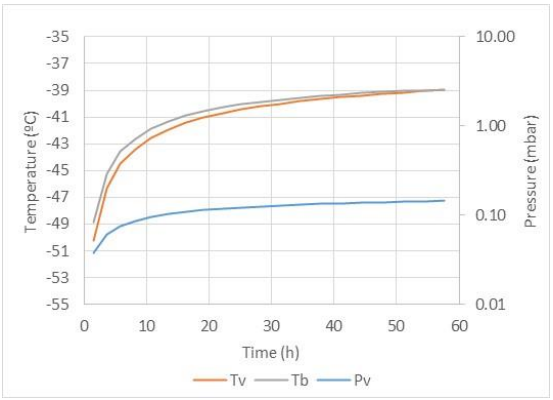

*Figure 3: Primary drying simulation with shelves temperature, Ts, constant at -30ºC and freeze dryer pressure, P, constant at 0.03mbar. Product 5% dissolution of sucrose **[5]**, vials ISO 6R **[3]**, filling height 10mm.*

The primary drying simulations, as it is showing the figure 3 (values of figure 3 between parenthesis), allows to know how from the initial pressure and temperature (Pv 0.03 mbar and Tv -50.26ºC) the sublimation front evolves during the drying (up to, Pv 0.146mbar and Tv -38.89ºC).

The product temperature at the vial bottom starts with a temperature difference with the sublimation front, due the conduction at the frozen product (-48.87ºC Tb, for -50.26ºC Tv), to be equal to the sublimation front at the end of the primary drying, as the frozen height is zero (Tb=Tv=-38.89ºC).

The maximum temperature at the product, both bottom and sublimation front, during the primary drying, occurs at the end (-38.89ºC). This temperature should not exceed the critical temperature for the concentrated product (mesh). As soon as the mesh is free of pure ice at its surroundings there is not risk of surpassing the critical temperature.

Nevertheless, before ending the freeze-drying process, some additional hours are commonly required at higher temperature and lowest vacuum, to remove fractions of unfrozen water that may be present (adsorbed) in the concentrated product. This last process is known as secondary drying and stablishes the residual moisture content of the final freeze-dried product.

High and low shelves temperatures. Effect of the chamber pressure on primary drying time.

Depending on shelves temperature the effect of lowering the pressure can be either beneficial or disadvantageous in terms of primary drying time, see table 3.

For low critical temperatures of the product, shelves need to be kept at low temperature (eventually below -30ºC), and then the most convenient approach is to keep the pressure as lowest possible to speed up the process.

P (mbar)	Kv (W/m2ºC)	Ts (ºC)	Pv max (mbar)	Tb max (ºC)	Primary drying time [h]
0.30	19.12	10	0.935	-21.35	12
0.03	12.34	10	0.517	-27.30	15
0.30	19.12	-30	0.331	-31.54	231
0.03	12.34	-30	0.146	-38.89	58

*Table 3: Simulation results at four scenarios: Pressures of 0.3mbar and 0.03mbar, shelves temperature 10ºC and -30ºC. Contact surface considered: 5m2, sublimation enthalpy 3850J/g. Product dissolution 5% sucrose **[5]**. Vials ISO 6R **[3]** Freeze drying height 10mm.*

Maximum temperature at the frozen product (it shall be noted that always occurs at Tb), is highly and mainly dependent on the pressure gradient at the dried layer. It is difficult to make generalizations of the shelves temperature range, that will make lowering the pressure beneficial for improving the process time.

The pressure gradient is specific of each product compound, as well as the size of the pure ice crystals. The size of the pure ice crystals surrounding the concentrated product is stablished during the freezing step, because of the cooling rate and nucleation temperature.

Nevertheless, it can be said that when the critical temperature of the product is above -30ºC, the thermodynamics of the process may advise to keep the pressure as higher possible, without exceeding the critical temperature.

When the critical temperature is below -30ºC, and the shelves needs to be at low temperature, then low pressures may be the convenient for the process.

In any case, it shall be noted that finding the proper package of excipients, that apart of making the freeze drying viable, increases the critical temperature close and above -20ºC, it is by far the most convenient situation, as the heat transfer between shelf and vial will be the best solution for the cycle (with higher pressures).

3. FREEZE DRYER IMPROVEMENTS

Minimum controllable pressure, freeze dryers prepared for working at low pressure.

The first step in freeze drying optimization, and for finding the proper process design space, is stablishing the limits of the freeze dryer, the minimum controllable pressure, that typically is around 0.05mbar **[6].**

Freeze dryers have not been historically designed to work at high sublimation rates with low pressures, as the optimum operating point was to use the maximum pressure without exceeding the critical point.

Perhaps the new challenges of the pharmaceutical industry will force to reconsider the initial design criteria.

Connection between the chamber and the condenser

The cross section of the connection between the chamber and the condenser is the most restrictive parameter for working at low pressures with high sublimation rates.

When working at low pressures the sublimation rates are lower than with higher pressures (Table 2). But the low density of the vapor is inversely proportional to the pressure and makes the flow between chamber and condenser with high velocity. The flow can be blocked (maximum), not being possible to reduce the pressure even if it is further lowered at the condenser. The only solution is increasing the diameter of the pipe (and valve) between the chamber and the condenser.

Condenser coils surface and temperature

The vacuum pump for the water vapor in a freeze dryer are the condenser coils, with its cold surface traps the vapor before reaching the vacuum pumps (that can only evacuate incondensable gases).

The typical minimum design temperature for the coils is -85ºC and its surface is designed two times larger than the shelves usable surface.

The ice grows in height at the coils where there is a temperature gradient making the external surface of the ice at higher temperature. Even with a good distribution of the coils, the only way to assure an effective trapping of all the water vapors, is having a good temperature margin with the sublimation temperature at the controlled pressure, table 1. For working at lower pressures, the minimum design temperature of the condenser may be reduced.

Although there exist mechanical refrigeration systems capable of providing temperatures below -100ºC (triple cascade, auto cascades), the pharmaceutical industry requires robustness and reliability (and why not to say it, standardization) that has made high consensus among the freeze dryer manufacturers to provide for industrial size freeze dryers, only double stage piston

compressors for up to 30m^2 (usable surface area) and screw compressors for above 30m^2 freeze dryers.

Liquid nitrogen refrigeration (-196ºC at atmospheric pressures) and new compressed air refrigeration systems (-160ºC) can be the alternative for the low temperatures with enough reliability compared to traditional mechanical refrigeration.

Vacuum system

The vacuum system (vacuum pumps) in a freeze dryer is reducing the pressure by emptying the air before the primary drying starts. When the desired vacuum level is reached, the vacuum system only evacuates the air/nitrogen coming from the controlled leak (vacuum control by a proportional valve) and the global leak of the chamber.

Typical minimum acceptance vacuum level for an empty freeze dryer is 0.01mbar. If controlling at low pressure is required the vacuum pumps may be enhanced by including and additional booster (roots) pump in series configuration, as also an additional leak valve, for low pressures.

4. FINAL COMMENTS

Notes about the author

Carlos Amor has been working with high vacuum and low temperature technologies for more than 10 years. He is graduated in Industrial Engineering and specialized in thermal energy, currently working for obtaining his Phd in freeze drying.

With over 10 years of experience on the pharmaceutical market: sales, process design and optimization, for freeze drying equipment and related machinery.

Founder of Lyoptimus Thermodynamics, he is specialist in simulation methods to optimize freeze drying processes. Focused on creative solutions for pilot scale batches for biologic drugs, and to adapt current processes to the new GMP Annex 1.

Additional notes from the author

The purpose of this document is recreative, as a summer reading, although written in the form of a scientific paper are only my thoughts and visions after two years of research, but of course nurtured by my years of working experience.

It is my intention in the nearest future to publish in scientific journals including some of the topics exposed in this document with the necessary rigorousness and detail.

In my current research I am freeze drying human platelets, which can be considered a biological pharmaceutical, where the key is preserving the bi-lipidic membrane, as it happens with other biotechnological pharmaceuticals. And if you are wondering, yes, I am facing low critical temperatures.

Figure 4: Carlos A. Amor

My intention has been to make a text both for the initiates and the experts, making a comfortable and interesting journey to understand what is happening during the freeze drying (specifically primary drying), but also giving some good innovative ideas that may interest the wisest in the field.

For sure I have been too much synthetic in some parts, and not rigorous enough in others. I ask the reader for his comprehension and if he has been reading so far, he is more than welcome to make me know about his comments/clarifications, please send me an email to: carlos.amor@lyoptimus.com

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