MILLROCK TECHNOLOGY

Use of a Small-Scale Freeze Dryer (MicroFD®) for Cycle Development and Optimization

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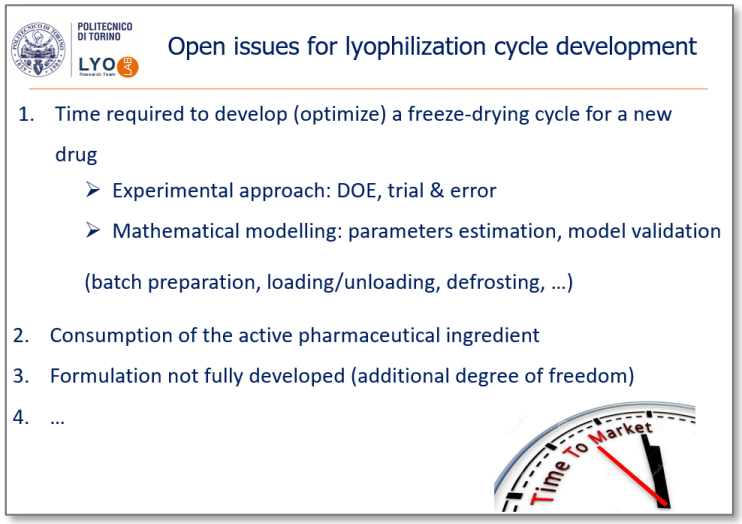
General issues regarding lyophilization cycle development include Time, API Consumption and Formulation Development. [Fig. 1] Time is required for the experimental approach for process design as well as carrying out the experiment. Design Of Experiments (DOE) and trial and error approaches take time. Even when using a mathematical model for process development, time is needed for experiments to estimate the parameters of the mathematical model and for the validation of the results obtained through mathematical modeling.

Time of the experiment includes not only freezing time, and the time for primary drying and secondary drying. Time is also required for preparing the batch; loading and unloading the batch; time for defrosting the condenser, cleaning the machine and setting up for the next batch.

FIGURE 1



In addition to time requirements, another concern of lyophilization cycle development is related to the consumption of the Active Pharmaceutical Ingredient. Even when lab scale freeze dryers are used for carrying out cycle development experiments, a significant amount of API is usually required.

It is not uncommon for API for experimentation to be costly or even unavailable in desired quantities. In some cases, formulation is not yet completely developed, thus adding complexity in developing a lyophilization cycle.

Millrock Technology solves or mitigates all these issues through the MicroFD®, a small-scale freeze dryer, specifically engineered for lyophilization cycle development. The MicroFD® minimizes batch preparation by replicating large run environments with very few vials.

The MicroFD® also reduces loading / unloading and condenser defrosting time. In summary the MicroFD® effectively reduces the cost for API substance, and the cost & time for protocol experimentation and technical transfer to pilot-production lyophilization systems.

Fig. 2 Here is a picture of the exterior and interior of the MicroFD®, where you can see the size of the batch. In this example 6R vials, 10mL, and 19 vials are loaded. For 20R vials, the system can work with as few as seven vials.

FIGURE 2

When a small-scale freeze dryer is used to develop a lyophilization cycle, information is collected regarding temperature, duration, critical process parameters and related lyophilization metrics.

The challenge is to have the evolution of the product be the same in the small-scale unit, as that of the larger commercial unit. Which is to say, the product temperature vs. time, residual amount of ice vs. time, drying duration and freezing conditions should be the same between the two pieces of equipment, lab freeze-dryer to production freeze-dryer. This is needed for the experiments conducted in the lab freeze-dryer to result in information applicable to the larger scale production freeze-dryer. The need for similar history and similar evolution dynamics of the product in the small-scale unit to the large-scale, primarily concerns the problem of heat transfer to the product.

The Problem

The evolution of the product in the small-scale freeze-dryer must be the same of the larger scale unit:

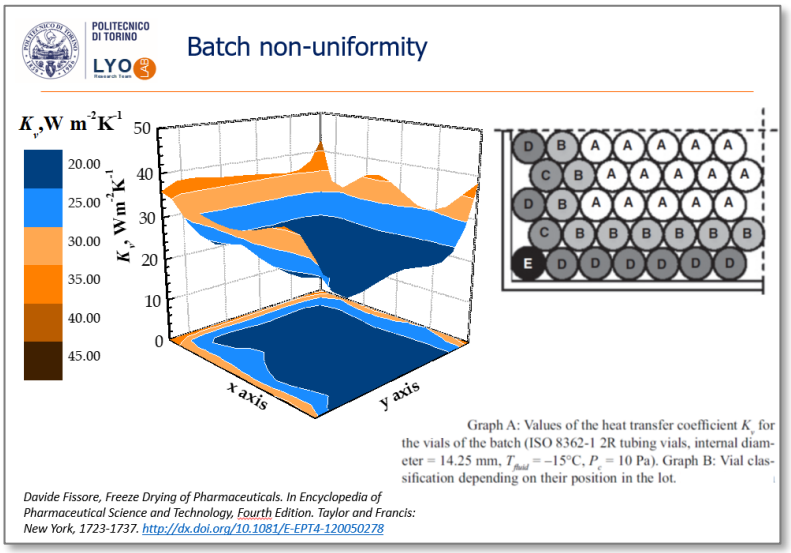
- Product temperature vs time
- Residual amount of ice vs time (drying duration)
- Freezing conditions

A primary problem is heat transfer to the product.

It is commonly known that the drying conditions in a batch of vials in a small or commercial scale freeze-dryer, are not uniform at all.

Conditions are generally distinguished between the so-called “center vials” and the so-called “edge vials.” [Fig. 3] The edge vials are the vials at the edge of the tray. They are not fully surrounded by other glass vials. These edge vials dry first in the batch and their temperature is higher than the temperature of the vials in the central part of the batch. This seems to reflect the fact that these vials receive heat from different sources and are not surrounded by sublimating vials.

FIGURE 3



Graph A: Values of the heat transfer coefficient K_v for the vials of the batch (ISO 8362-1 2R tubing vials, internal diameter = 14.25 mm, T_{fluid} = −15°C, P_c = 10 Pa). Graph B: Vial classification depending on their position in the lot.

Davide Fissore, Freeze Drying of Pharmaceuticals. In Encyclopedia of Pharmaceutical Science and Technology, Fourth Edition. Taylor and Francis: New York, 1723-1737. http://dx.doi.org/10.1081/E-EPT4-120050278

<u>It is often considered that the source of heat is being radiated from the freeze-dryer’s chamber walls. This surely plays a role in the system but there are other factors which have a greater effect</u>.

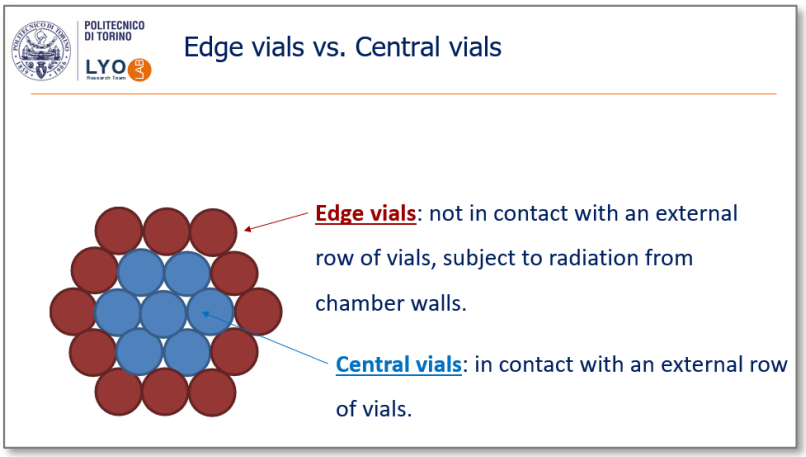
The problem with creating the same evolution of product within a small-scale freeze dryer as that of a large scale is that, with any batch of vials, there are not uniform drying conditions. Part of the batch receives additional heat. The temperature is higher in these vials and they dry faster.

Usually we consider the Kv, the heat transfer coefficient from the shelf to the product in the vial. Vials at the edges of the shelf are characterized by a higher value of this coefficient with respect to vials in the central part of the batch.

This is what occurs in a commercial scale lyophilizer. How does this differ from a small-scale unit? The problem is related to the fact that in the small-scale unit, a larger portion of the vials are edge vials.

[Fig. 4] For example, in this sketch of the batch of 19 vials, we have seven vials that are like central vials, and we have 12 vials that are edge vials. In the commercial-scale unit, edge vials may be 2% or 3% of the whole batch. In a small-scale batch, edge vials can be 50% or even more, and this will strongly affect the results that you can get in a small-scale system.

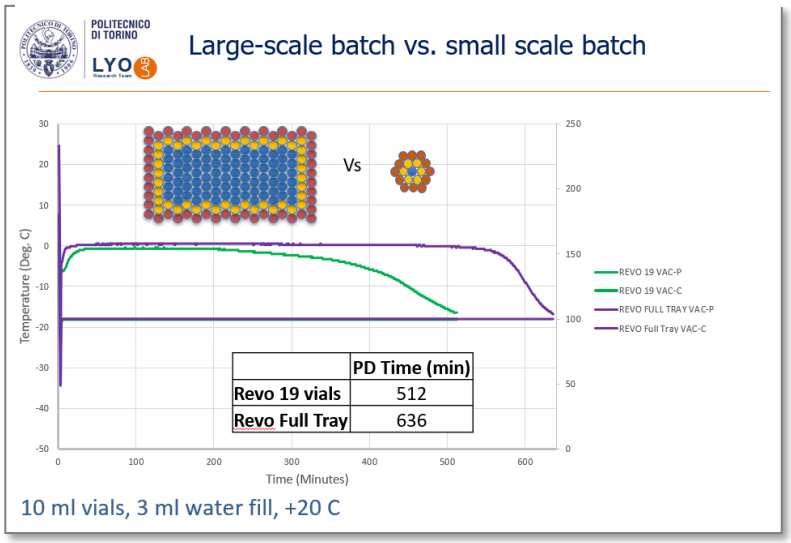
FIGURE 4



Let's consider a case study of a small and full tray run, within the same pilot scale freeze-dryer. [Fig. 5] In this diagram, we compare runs within the same pilot scale unit, a Revo® freeze dryer. In one case, a full tray test. In the second test, just 19 vials in the same Revo® freeze-dryer.

What we see is the trend of the Pirani signal in the system constant for most of the primary drying stage, and then when drying moves to the end, the signal decreases, and when we are close to the end, it becomes equal to the signal of the capacitance manometer. [Fig. 5] The purple line refers to the full tray situation, and the green one refers to the 19-vial batch. This poses a problem, because, working with a pilot scale dryer it is desired to save time and API. Therefore, instead of loading a full tray, 19 vials are loaded, for a drying time of 512 minutes.

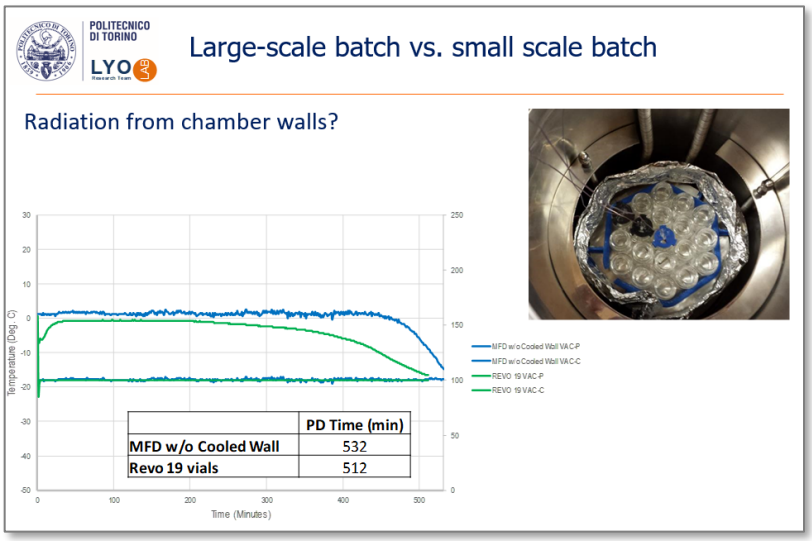
FIGURE 5



But, 512 minutes is not at all representative of what will take place in the same pilot system with a full tray. In that case, drying time is about 10 ½ hours. By using 19 vials, time may have been saved and API saved, but the small-scale batch results and temperature dynamics are not representative of what will occur with a full tray.

Why is this so? If we understand the reasons, then we may do things to counteract the differences enabling us to utilize lower sized batch runs to gain protocol direction for larger batches.

FIGURE 6

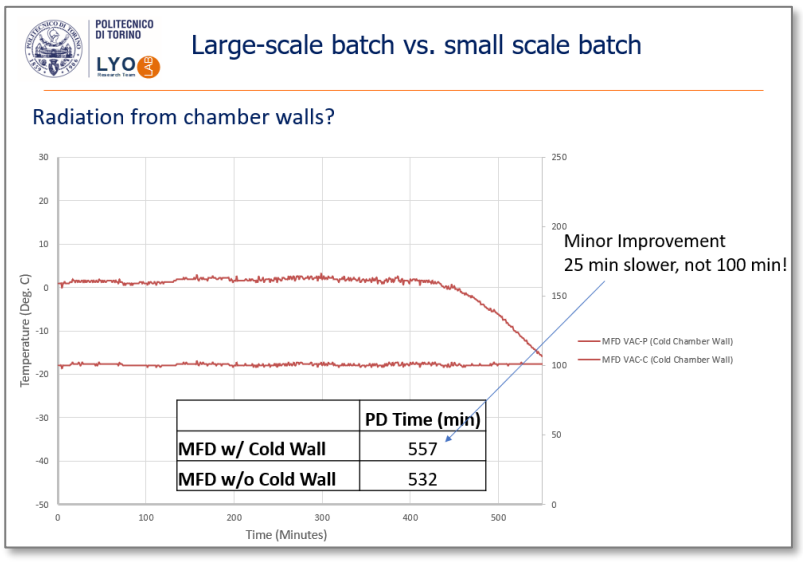


Is the difference in vial temperature due to radiation from chamber walls? Is the effect of radiation that heats the edge vials in the small-scale batch, increased by the number of edge vials present?

We performed the same test in a prototype MicroFD® because the prototype MicroFD® enabled us to manipulate the temperature of the chamber walls.

Fig. 6 First, we carried out an experiment with the 19 vials in the MicroFD® and we found a drying time that was about 532 minutes. This is very close to the 512 minutes we obtained with the 19 vials in the pilot Revo® freeze dryer. So, we may say that the processing event of the 19 vials in the Revo® and the MicroFD® are similar.

FIGURE 7



In the second test, we decreased the temperature of the walls dramatically, to -20 and even -30°C.

If the reason for higher temperature and shorter drying time is radiation from the chamber walls, we may reduce the temperature of these walls in order to minimize this effect.

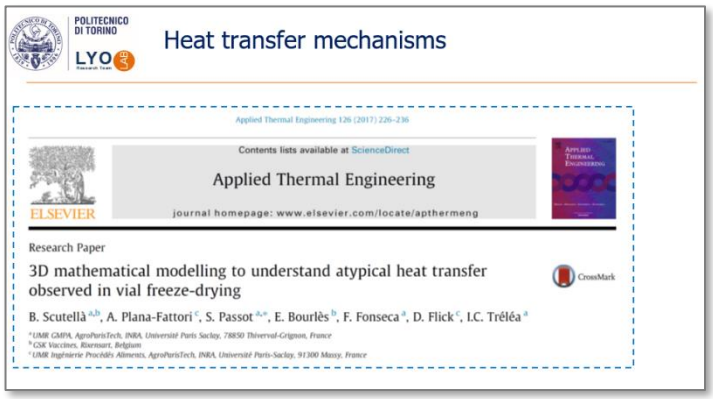
With a colder wall, drying time slightly increased. Fig. 7

We moved from 532 minutes to 557. But remember, in the full tray experiment, drying time was 10 and ½ hours. So, while radiation plays a role, it is not the main cause of the edge effect. By cooling the wall to eliminate radiation, we were not able to completely reduce the effect, only make a minor improvement.

Two years ago, Bernadette Scutellà and coworkers published data on Applied Thermal Engineering. Fig. 8

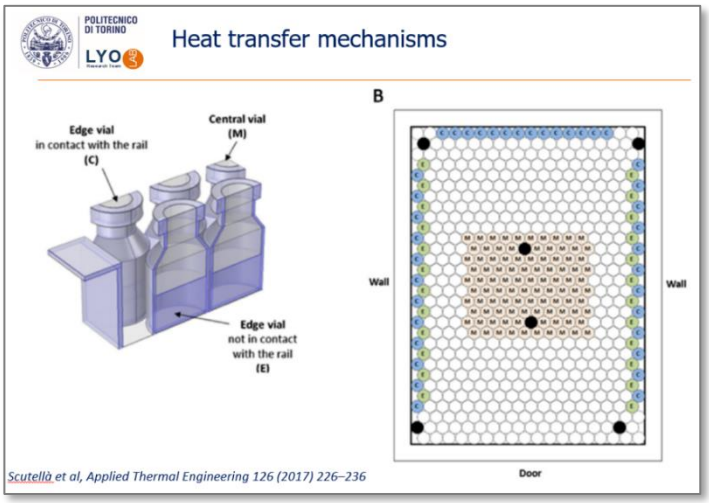
Their research paper focuses on three-dimensional mathematical modeling of heat transfer to product in vials during the freeze-drying process. It is very different to measure experimentally, rather than through mathematical modeling, the contribution of radiation and conduction. It's much easier to carry out a study through mathematical modeling to understand the heat transfer.

FIGURE 8



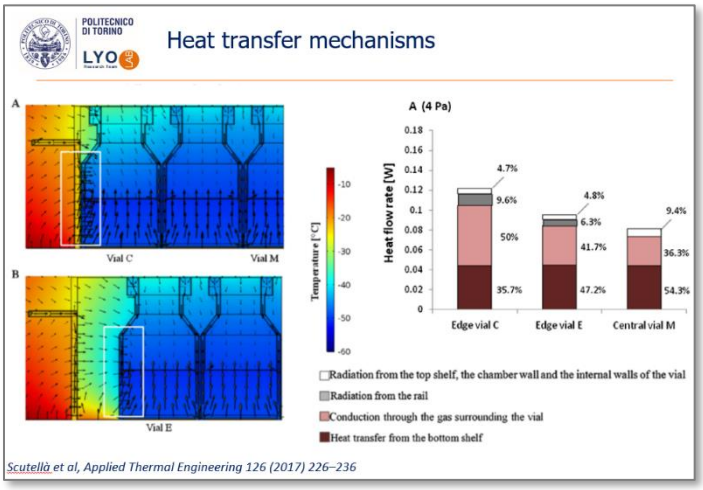
This is the consideration they investigated: A full-scale batch with a metallic frame surrounding the vials. [Fig. 9] They identified different type of vials in this batch. The central vials and the external vials in contact or not with the metallic frame.

FIGURE 9



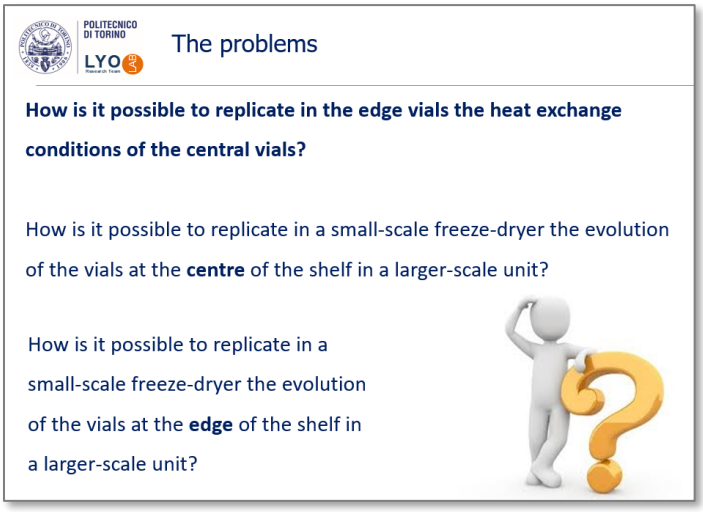
They concluded that in both type of vials, central vials and those vials in contact or not with the metallic frame, there is a certain heat transfer from the bottom shelf and this contribution is the same. The water sublimated per square meter is the same.

FIGURE 10



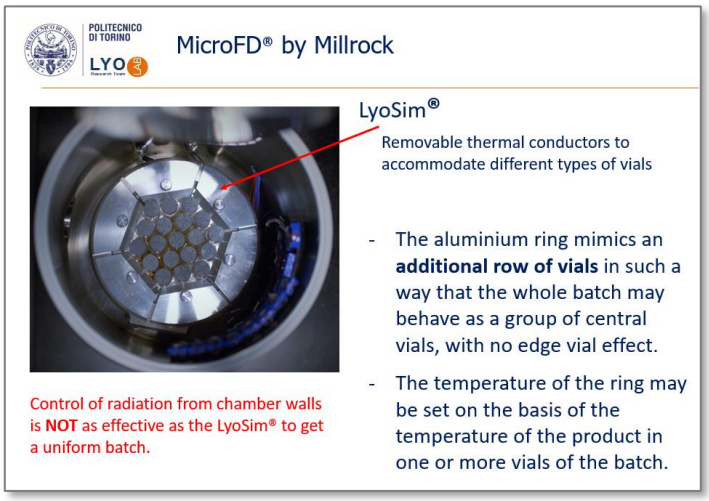
Then you have contribution by radiation. [Fig. 10] Radiation from the top shelf, the chamber wall and radiation from the rail. The contribution of this radiation is very, very, very small. It's a contribution of the conduction through the gas surrounding the vials, particularly in the edge vials. In the central vials, each vial is surrounded by other vials. In the edge vials, each vial is just partially surrounded by another vial. Part of the vial is exposed to the gas in the chamber and the endothermic event of the surrounding sublimating vials is not present.

FIGURE 11



We know the transfer mechanism to the vials in the batch. [Fig. 11] How can we replicate in the edge vials the same heat transfer condition of the central vials in order to get a uniform system? How is it possible to replicate, in the small-scale freeze dryer, the evolution of the vials at the center of the shelf of the larger-scale unit?

FIGURE 12



We are interested in these vials because they are the majority of the batch. 95 or 96% of vials are central vials. The duration of the time of drying is related to the dynamics of the system in these vials.

Fig. 12 To replicate the evolution of the vials, the MicroFD® is equipped with LyoSim®. LyoSim® is a system that is comprised of an stainless steel ring whose temperature may be controlled independently from the temperature of the shelf. The software that controls the MicroFD® and LyoSim® allows the operator to indicate an "Offset Value" that enables the ring to produce the same conditions as center vials.

The "Offset Value" is the difference between the temperature of the ring and the temperature of the product in one or more vials of the batch.

Removable aluminum thermal conductors are placed in the system and used to guarantee a contact between the external vials of the batch, the edge vials, with the LyoSim® heating mechanism. In this system, Millrock Technology is not using radiation to control the heat transfer in the edge vials. Instead, heat transfer is controlled by an aluminum ring in contact with the external vials of the batch. This enables full control of the process.

FIGURE 13

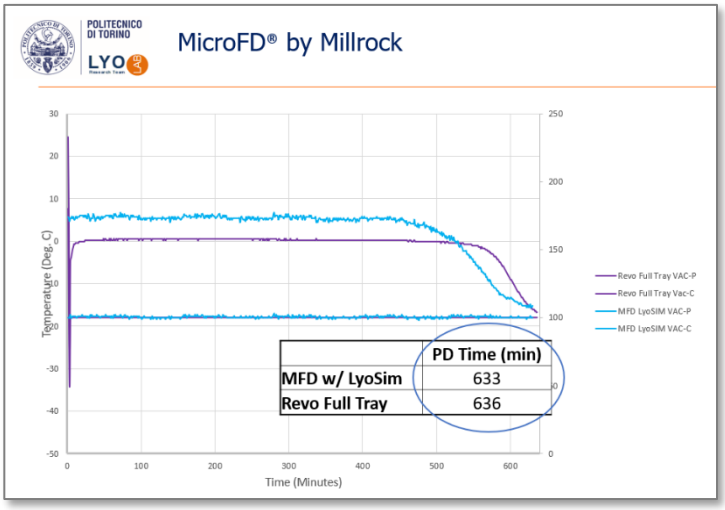
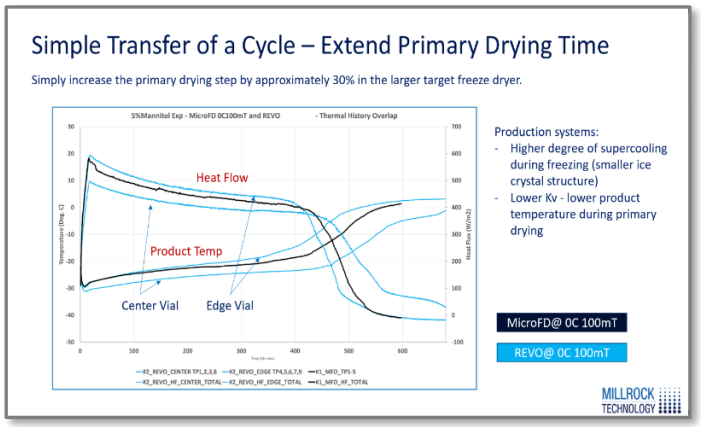


FIGURE 14



The ring has the task to mimic the temperature of an external additional row of vials and does so in a highly efficiently and effective way.

Fig. 13 Using the LyoSim® tool, the drying time we get in the micro-scale freeze dryer is 633 minutes. That is very close to the value obtained in the larger pilot freeze dryer, "The Revo®" with a full tray.

This indicates that the metallic ring, "LyoSim®" can effectively reproduce an additional row of vials where sublimation is occurring, with a certain temperature, and so compensation is made for the anomalous heat transfer mechanics typical of the edge vials.

FIGURE 14

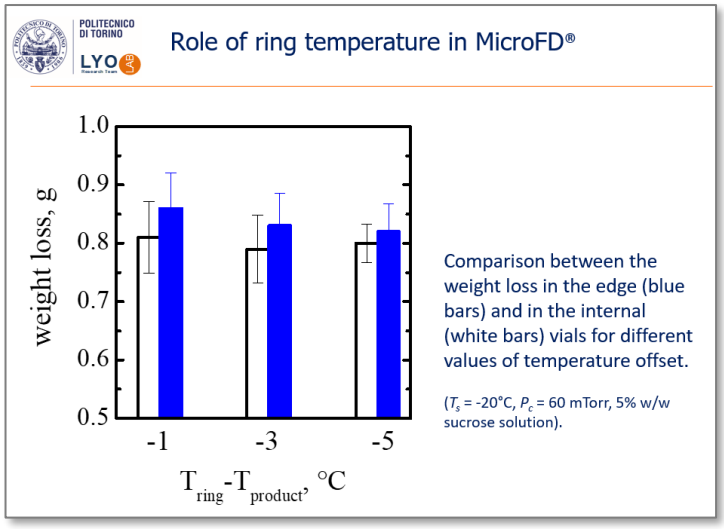


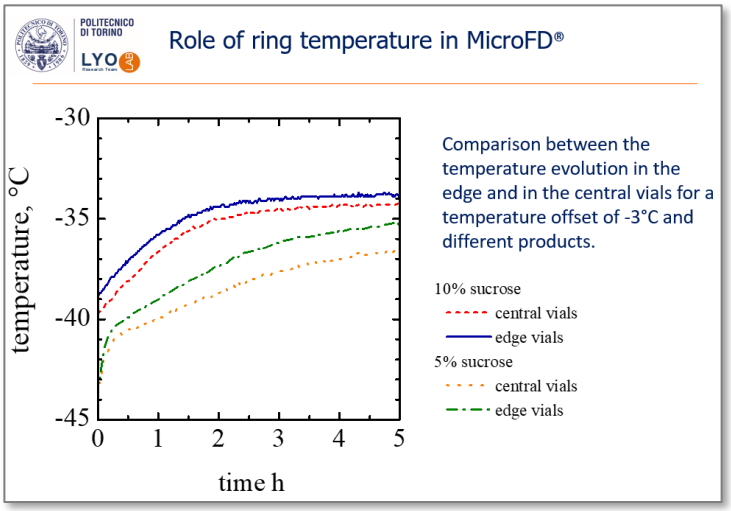
Fig. 14 Selection of the temperature of the LyoSim® ring increases the degree of freedom of experimentation. An experiment may be carried out with varying pressure and temperature, but the MicroFD® (freeze dryer) equipped with the LyoSim® delivers an additional degree of freedom, represented by the temperature of the ring, or by the offset value.

The temperature of the ring tracks the temperature of the product based on the value of this offset.

A fast test may be carried out using just water or water with an excipient. A batch of vials with water, or water with sugar if you prefer, is prepared. The temperature of the ring is selected, this is the offset value. Then freezing is carried out and then sublimation for four or five hours. At the end of the five hours, the weight loss in the batch is measured. Obviously after five or six hours of drying, the ice sublimation is not completed, and so we can measure the homogeneity of the system. Fig. 14 In this diagram, we compare, for example, the temperature offset of minus one (-1 C) and weight loss in the central and edge vials. The blue bar is the weight loss in the edge vials while the empty bar is the weight loss in the same area in the central vials.

The test is repeated for minus three Celsius (-3 C) temperature offset, then minus five, and we see for example, for a temperature offset of minus five, the offset in central and external vials is very, very close. This indicates that minus five (-5 C) may be a good value of offset to select and set the ring temperature.

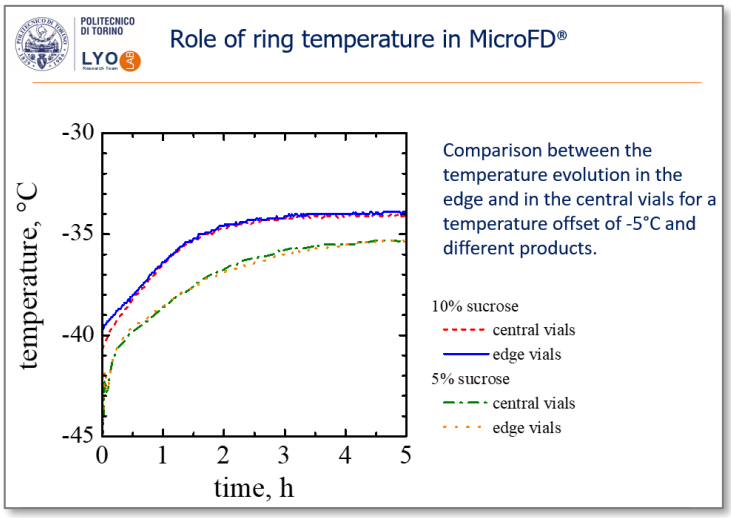
FIGURE 15



In addition to weight loss, the temperature of the product is considered. [Fig. 15] This diagram shows the evolution of the temperature of the product in edge and central vials in the Micro Freeze Dryer (MicroFD®), with the 10% or 5% solution.

In the case of a temperature offset of minus three (-3 C), there is a certain agreement, but in case of a temperature offset of minus five, [Fig. 16] the temperature measured in the edge and in the central vials is very, very close. So drying rate is uniform and product temperature is very, very close. Usually minus three (-3 C), minus four (-4 C), minus five (-5 C) may be considered as good starting values. This type of preliminary experimentation is used for setting and optimizing the temperature of the LyoSim® ring.

FIGURE 16



Starting with -5°C, very nice results are usually obtained. Temperature offsets of -1 C, -2 C, -3 C, etc are used for optimization, the goal being to mimic in the edge vials the evolution of the central vials. This is accomplished by removing heat from the external vials, to compensate for heat sources such as radiation and conduction. The temperature of the metallic element should be slightly lower than the temperature measured by thermocouples in the central vials to simulate the sublimating vials.

FIGURE 17

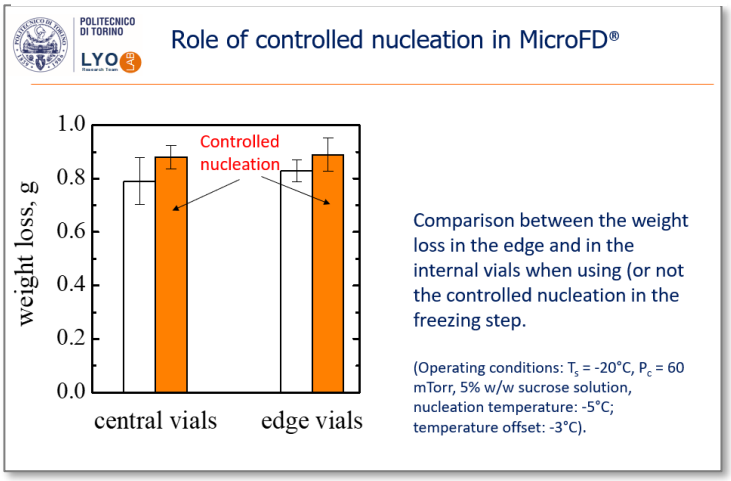
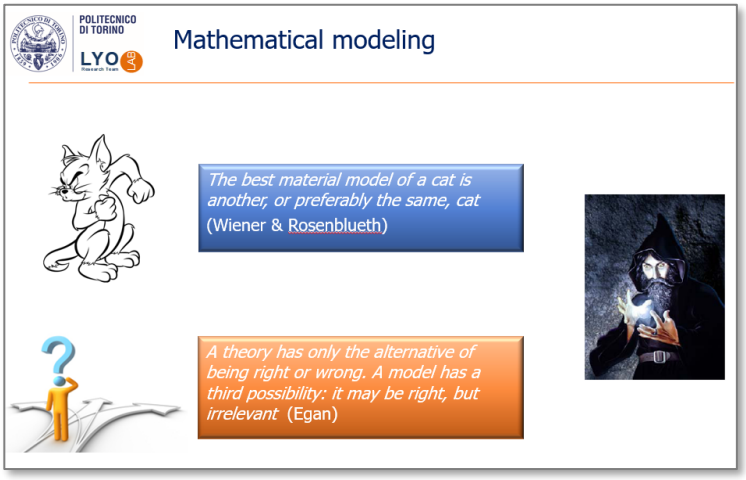


Fig. 17 In the MicroFD® you may also use controlled nucleation techniques, in particular, the FreezeBooster® ice fog technique. Water is sprayed in the condenser forming a spray of ice fog that is then moved to the chamber where it initiates nucleation. If you are employing controlled nucleation in either a pilot or manufacturing scale, in order to get representative results, you will need to do the same MicroFD®.

FIGURE 18



Using controlled nucleation further reduces the heterogeneity of the system helping to obtain a uniform batch, even at a small scale. Ice nucleation creates an important role that is not to be neglected.

Fig. 18 You may need to perform experiments to determine the values of model parameters, because you want to use mathematical modeling for several issues. For calculating the design space, for performing offline calculations, the optimization of the process in such a way that then you go on the machine just to check or verify the results of the mathematical model.

For sure, all mathematical models are wrong. It is not possible to write an equation to account for all the heat and mass transfer, momentum transfer phenomena that occurs in the system. But some mathematical models are useful.

FIGURE 19

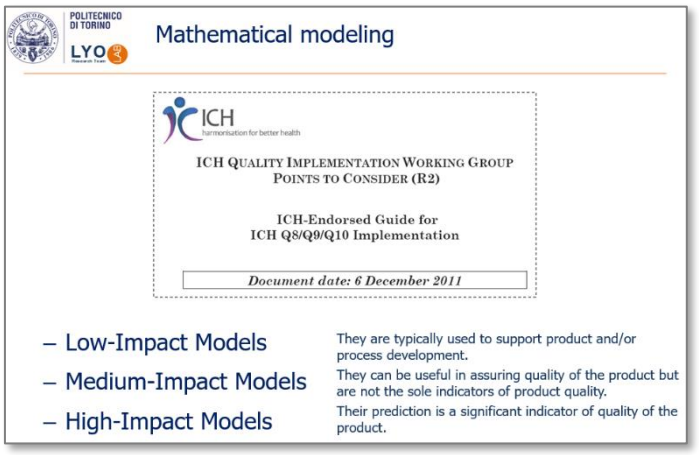


Fig. 19 We are not using what we refer to as a "high-impact model." Instead, we are using, in the framework, "low-impact models." These low-impact models are used to support product and/or process development. We use a model to perform the calculations, but we must check the results of the calculations. The models alone are not the sole indicators of product quality. They are not high-impact models.

FIGURE 20

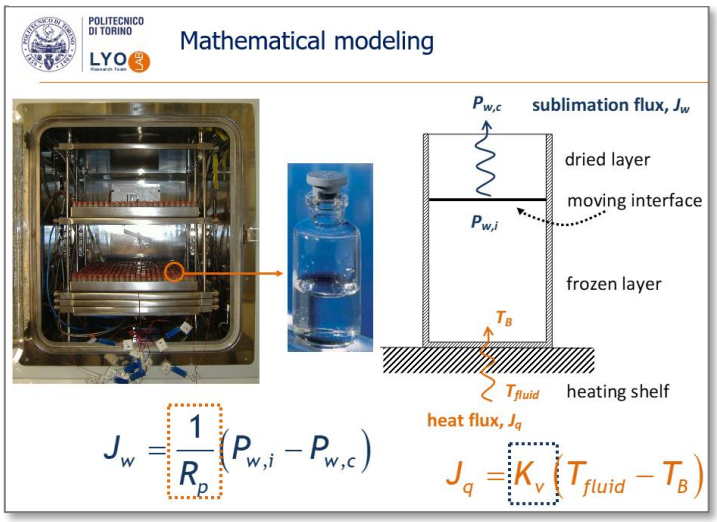
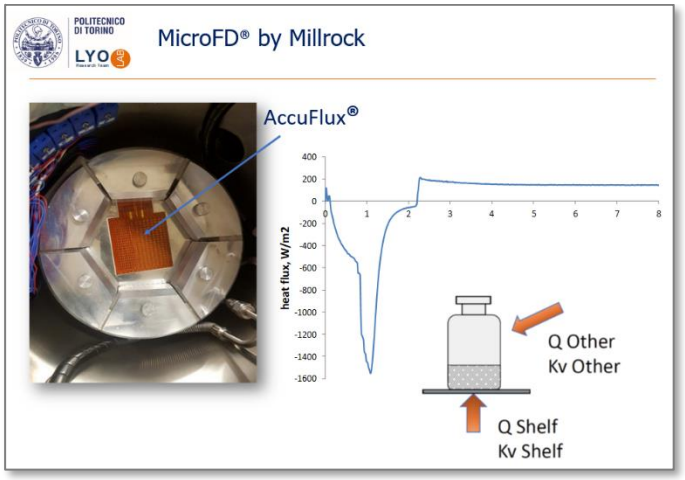


Fig. 20 The low-impact model usually used in this framework is the typical one-dimensional model that assumes a frozen layer, a dried layer, and an interface separating the two layers that moves from the top to the bottom of the product as drying goes on. In this framework, the heat transfer to the product is assumed to be proportional to the difference between the temperature of the heating fluid and the temperature of the product. Kv is the heat transfer coefficient parameter we need to get. With respect to mass flux from the interface of sublimation to drying chamber, it is written using the equation shown in this diagram. Fig. 20 It is assumed to be proportionate to the difference between partial pressure of water in the interface of sublimation and partial pressure of water in the drying chamber. The parameter in this case is Rp, the so-called resistance of the dried cake. So, we need to get Kv and Rp.

Fig. 21 In the Micro freeze dryer, we have a very important device called AccuFlux®. AccuFlux® is a sensor that measures the heat transferred to the product from the shelf. Here you may see a typical trend of the heat flux to the product during a drying cycle.

You may see the cooling, the nucleation, and then when you add heat to the product during the primary drying.

FIGURE 21



In so doing, you monitor the flux, the temperature of the product and that of the shelf, and so using the definition of Kv, illustrated in Fig. 20, you may immediately get the value of Kv. But you need to pay attention to one issue. In this model the dynamic is very simplified as all the heat is transferred from the shelf. This, however, this is not what occurs in a freeze-dryer. In a freeze-dryer, you have heat transferred from the shelf and transferred from the surrounding. Referencing Fig. 10, we see that the heat transfer from the shelf is only part of the heat totally transferred to the product.

Fig. 21 With AccuFlux®, you measure just the heat from the bottom. So, you need to pay attention when using this Kv for process development and for process innovation, because this is just the Kv from the bottom. The software labels it as "Kv Shelf". We will see later that at the end of a full cycle Kv total is automatically determined by the software.

FIGURE 22

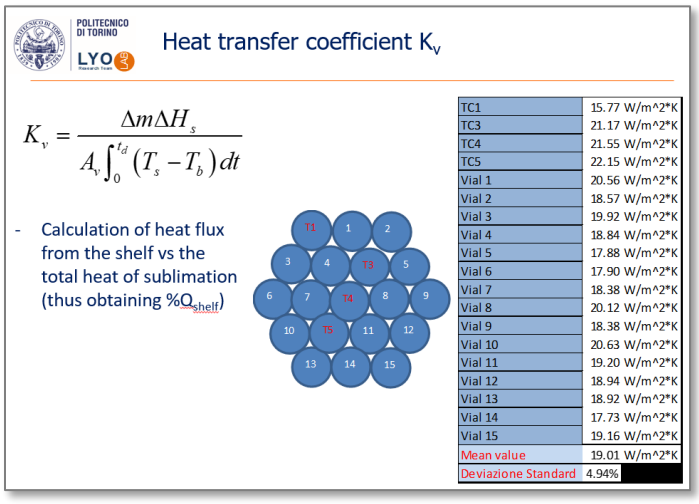
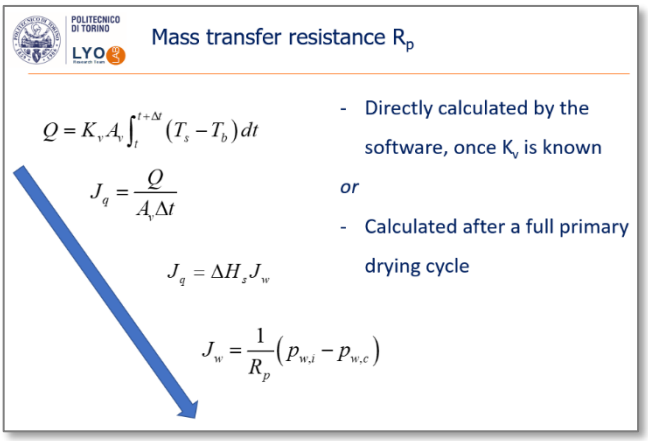


Fig. 22 When you perform two or three gravimetric experiments with different values of ring temperature offset and, if you measure the weight loss before and after the ice sublimation you can easily determine Kv.

At the end of the gravimetric experiments you get information about the delta M (mass) in edge and center vials and you get information about temperature of external and central vials, and you may easily, then, calculate the Kv .

FIGURE 23



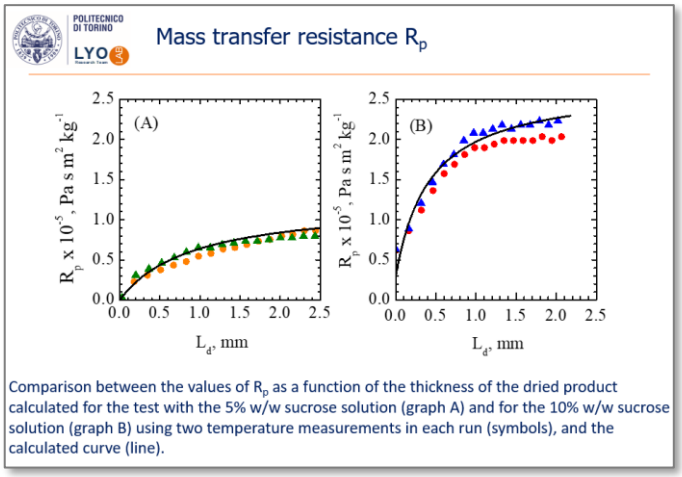
You may calculate by this way the percentage of Kv of heat recieved by the vials from the shelf. Once you have this value for the future, you may put it in the software, and it will automatically correct the estimated data obtained by AccuFlux.

Fig. 23 Rp is calculated on basis of the definition. In order to calculate Rp, you need to know sublimation flux.

Sublimation flux is calculated by the heat flux because from the energy balance at the interface of sublimation, the sublimation flux multiplied by the heat of sublimation is equal to heat flux.

Once you know the heat flux, you know also the mass flux. And once you know the mass flux, chamber pressure and the product temperature, the very easy calculation gives you the value of Rp.

FIGURE 24



Comparison between the values of R_p as a function of the thickness of the dried product calculated for the test with the 5% w/w sucrose solution (graph A) and for the 10% w/w sucrose solution (graph B) using two temperature measurements in each run (symbols), and the calculated curve (line).

Fig. 24 Here is an example of a trend obtained of Rp. Rp is not a single value. It's a function of the thickness of the dried product obtained for 5% sucrose solution or for 10% sucrose solution, and so on. Also, Rp is quickly obtained at the end of a test carried out in the system without using any additional Process Analytical Technology.

So, the first point in this presentation was batch homogeneity. Second point is obtaining Kv and Rp useful for optimization. The third issue is using the small-scale unit for reproducing the process of large-scale unit to perform scale-up and scale-down.

FIGURE 25

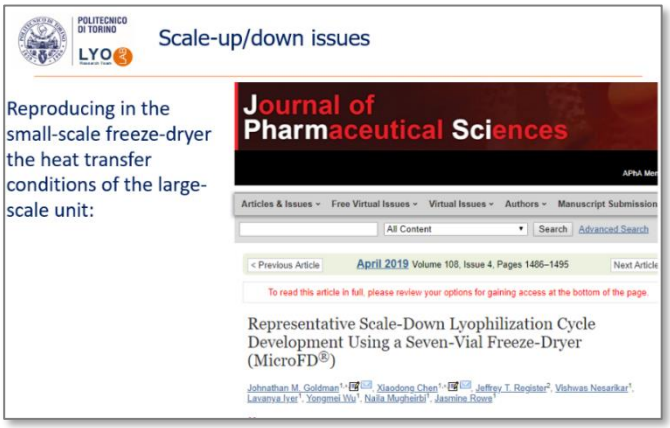


Fig. 25 This paper appeared in the Journal of Pharmaceutical Sciences in April 2019 and is the first paper where some results on this topic are summarized. This paper considered two units, the MicroFD® and the Lyostar III. They performed in the Lyostar III, this problematic test for obtaining the Kv values in the whole batch. Edge vials, central vials, second row vials, and so on. Here you may see different colors indicating different values of this Kv. Fig. 26 Then they moved to the small-scale freeze dryer and they modified the temperature, the offset temperature. So, the temperature of ring. **Fig. 26** In the right part of this diagram you see that depending on the temperature of the ring, you may reproduce in the MicroFD®, the dynamics of the product in the other unit.

FIGURE 26

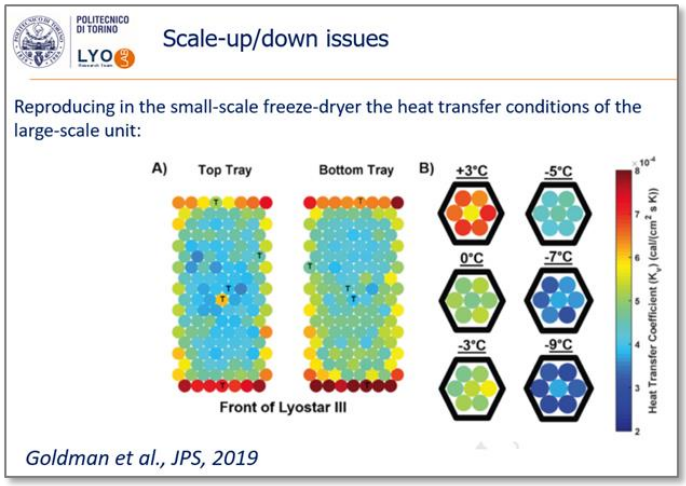


Fig. 26 With -5 C, you obtain the dynamics of the central vials. The -5 C is in all cases a good starting for obtaining MicroFD® dynamics of the central vials of a large unit.

Then if you move, for example, to zero, to +3 C. +5 C, you may reproduce in the small-scale unit the behavior of edge vials in the larger-scale apparatus. If you are interested in the happenings of the central vials, in most of your batch, you just look for batch homogeneity in the MicroFD®. You don't need to carry out a lot of work and experiments. Just optimization of the ring temperature, but no more than that. Where you can start with an offset temperature of -3 C or -5C and we will get a good result.

If you would like to reproduce also the story of the edge vials, in this case, you need to characterize, for example, through a gravimetric test using just water, not the active pharmaceutical ingredient, the pilot

scale unit, because the story, the dynamics of the edge vials, is influenced by the characteristics of the equipment. So, it is not possible to generalize this type of trend.

FIGURE 27

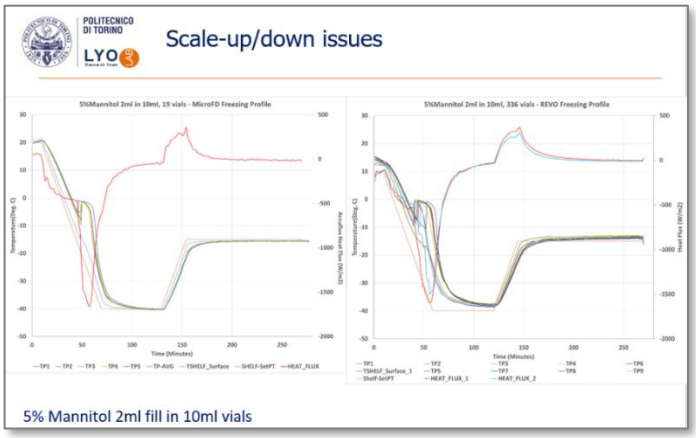
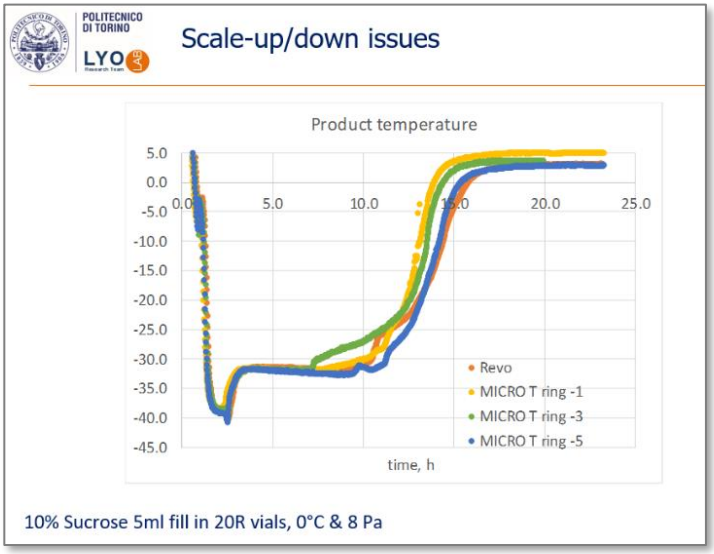


Fig. 27 Here is an example of the evolution of the product. 5% mannitol in 10mL vials in the REVO® pilot-scale unit on the right, and in the MicroFD® on the left. We see the evolution of the heat flux on the shelf and the evolution of the temperature. Here the ring offset is -5 C and the agreement is almost perfect.

Fig. 28 Here is another example: 5% sucrose in 20R vials at Zero Celsius and eight Pascal. Orange point refer to research of being in the Revo® pilot-scale unit, and the other few refer to the temperature of the product in the MicroFD® with different temperatures of the ring. We see that agreement between these temperatures is very, very good. Even if you do not optimize, you do not have to spend time optimizing the temperature of the ring, so you start with let's say -3 C or -5 C, the product temperature is noticeably very, very close to that obtained in the commercial-scale unit.

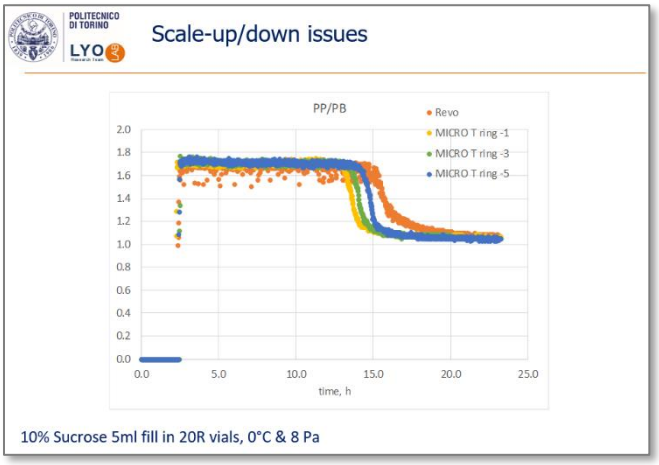
FIGURE 28



After a certain point, the temperature measured by thermocouple will not be representative, for many reasons, of the product. When the thermocouple is no longer in ice it moves to the temperature of the heating source. We are addressing the first part when the temperature is flat, corresponding to the equilibrium between the heat to the product and the heat used for the sublimation.

Fig. 29 Here you can see the comparison of the ratio between the Pirani and Baratron pressure curves obtained in the Revo® pilot-scale freeze dryer and in the MicroFD® for – 1 C, -2 C, -3 C of temperature offset (of the LyoSim® ring.) In the decreasing part, the slope is different Revo® to MicroFD®, because this slope is strongly dependent on the size of the batch. But if we focus, PP/PB is the ratio between Pirani and Baratron pressure

FIGURE 29



thickness. It's a curve that is quite frequently used to assess and to identify the endpoint of the primary drying. Baratron is a capacitance manometer sensor so it measures the true pressure of the system. Pirani sensor is another type of sensor that measures pressure, but its measurement of pressure is strongly influenced by water vapor.

At the end of primary drying, when there is no more water vapor in the chamber, the two signals overlap. Previously you have a certain ratio that is around 1.6, 1.8, which is the endpoint that some may consider to be the midpoint (consider the decreasing trend). Other people consider when the curve starts decreasing. However, when the two curves overlap, drying is completed. With the Pirani over Baratron, we are not measuring the amount of ice for ending of the sublimation, we are measuring the total disappearance of water vapor through the drying chamber, but actually the two situations are not so different.

In any case, if we have a look at these results, we may see that using a temperature ring of -5 C will have less than a one-hour difference between drying time obtained in the MicroFD® and in the Revo®.

We recently completed, a few hours ago an experiment with -7 C, but I was not able to add this curve to the graph. With -7 C, the two Pirani and of Baratron curves of Micro and Revo perfectly overlap. So, with -5 C as the starting point, results are more than acceptable. In the MicroFD®, the similar graduation and similar product temperature and various model parameters may be used for offline calculations. The MicroFD® software allows the optimization the drying condition in a single run. It calculates time by a method used for calculation of the Baratron. The Baratron is calibrated in air. There is a surface membrane of the Baratron and when it's in contact with an environment at a certain pressure, the deformation of this membrane modifies electrical properties. The pressure determines the deformation that determines the modification of the capacitors of an electrical circuit.

The Baratron operates only by pressure regardless the composition of the gas in contact with the membrane. The Pirani, however, is calibrated in a gas. It's a different measurement principle. Pirani is composed by a filament, a metallic wire that is heated through voltage, and the pressure is determined by a difference of voltage. The temperature of the filament wire is a function of the pressure and the composition of the environment surrounding this wire.

If this wire in air at a certain pressure for a certain voltage, you will get a certain temperature. If this wire is put in an environment filled with water vapor, under the same pressure, the thermal conductivity is different and so the temperature will be different. Because the sensor is calibrated in a gas, it is unable to recognize the concentration of water vapor, and so it will produce a pressure value as if it was still in the calibration gas, which will not be equal to the absolute pressure. This is useful, because it

indicates when water concentration in the chamber starts disappearing as the pressure indicated by Pirani sensor moves closer to that of the Baratron capacitance device. Fig. 30 In conclusion, MicroFD® With LyoSim® and LyoPAT® does more than larger lab freeze dryers do and with fewer vials. The MicroFD® provides all critical process parameters AND provides heat flux measurement utilizing AccuFlux®. Using significantly fewer vials (i.e. 19 vials if using a 10R serum vial) means you use less active pharmaceutical ingredient and you save time and money with extensively shorter set-up and downtime.

Special features of the MicroFD®:

- Takes the guesswork out of protocol development
- Uses less of your valuable product for R&D
- R&D and cycle transfer with as few as 7 vials
- Determines Kv, Rp and other critical process parameters

For more details about the MicroFD® please visit the MicroFD® section of Millrock Technology's website: https://www.millrocktech.com/freeze-dryers/microfd-small-research-freeze-dryer/

FIGURE 30