From MicroFD® to "Macro" freeze-dryers and vice versa - transcription

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My name is Davide Fissore. I am a full professor of chemical engineering at Politecnico di Torino. Politecnico di Torino is a university in Italy, in the northwest of Italy. I work in the field of freeze-drying. In particular, I am interested, I'm active in the field of modeling freeze-drying process. In particular, the development of a model useful for process optimization, for process control, for process metering, for sys control, for cycle development, cycle transition, development of new systems for non-invasive monitoring of the freeze-drying process.

So, this is the general framework of my activity at Politecnico di Torino. Not just my activity, because here we are in a quite large group, with my colleagues Antonello Barresi, Roberto Pisano, and with several PhD candidates, postdoc, master students working on their project. So, it's a pleasure for me to be here today, and to meet virtually, in this moment, so many people. I would like to invite you to use the chat for asking questions, because microphone is mute for most of you. And so just to avoid switching on, switching off microphone and so on, you may use the chat in every moment when you have questions. If and able, I am answering your questions probably during my talk, or at the end.

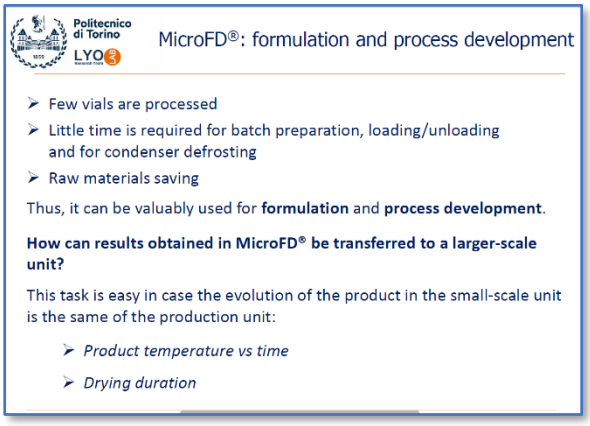
Today, the main topic of this webinar is MicroFD. So, first questions I would like to pose to the participants, is just if you have ever used this equipment, this freeze-dryer? I do not know. Has any one of you used it for process development, for conducting cycles in this gap, the micro freeze-dryer? Or it's something completely, completely new? Just also to tune my talk. May use the chat if you want. So, one is using it, okay. Well, it seems for most participants, it is something new.

So, I would like, today, to give you framework about the use of this apparatus, about 35 minutes. I will try to give you some take home messages at the end of this webinar. MicroFD, Micro Freeze-Dryer is a freeze-dryer, first of all. You may use it to carry out freeze-drying cycles in your lab, to investigate the effect of operating conditions of formulation characteristics, compositions, and so on. And at the end, after the study, you need to transfer this result, this information to the production freeze-dryer.

This is what you usually should do in your lab, using other freeze-dryer, other lab scale, freeze-dryer or pilot scale yield. But in this case, you may have some specific advantages for this. In this sense, we can move from MicroFD to Macro freeze-dryer, and then to large scale yield. But we may do also vice versa. I mean, we can move from Macro freeze-dryer, from large scale unit to Micro Freeze-Dryer. We may try to replicate in MicroFD the heating conditions to prove that we experience in a different type of apparatus. So, we will see these two ways for using this equipment.

This is MicroFD. As you may see in the picture on the left, is a very small apparatus. It is a very small freeze-dryer. The chamber, shown in the picture on the right, may holster seven vials, if you are using 20R vials. Or like in the case shown in this slide, nineteen vials. In this case, 10R vials are loaded in the freeze-dryer. You may load even a higher number of vials. Obviously, in case the vial diameter is smaller. But in many cases, the number of vials, the size of the batch that you process is significantly lower than the size of the batch of an industrial scale freeze-dryer. Or even of a pilot scale equipment.

The fact that few vials are processed is an especially important issue, because it allows, first, saving time. Little time is needed for batch preparation, batch loading, batch unloading, for condenser defrosting. All these types need few time, in this case. But which is the most important issue, from my point of view, is that this way of carrying out experiments allows to save raw materials. Because this is a critical issue in case the cost of the raw material is high, the availability of raw material is not sufficient to load a pilot scale dryer. Or even in case of the formation has not been fully, fully developed.

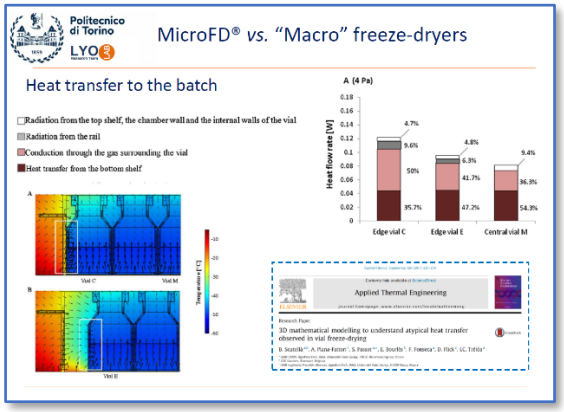


So, you may use MicroFD for both formulation and process development like all the other pilot scale unit, with important advantage that you save raw material and that you save time. But there is a second important issue, because obviously, when you carry experiments process development ... What I mean for process development, I mean that you modify, you change the values of shelf temperature,

the value of channel pressure, and you want to see which the effect of the change, the effect on final product qualities, the effect on duration of the drying stages.

Okay, you may do it with very low amount of raw material. But it's a second important issue that has to be taken into account, and that MicroFD allows you to explore it, at least the problem of process transfer, or process scale up. As I told you before, in all cases, you conduct experiments in a pilot scale unit in your lab. And then you need to move to a manufacturing scale, you need to change something in your approaches. You need to modify drying duration, you need to modify to change the value of the operating conditions in such a way that what occurs, what we occur in the manufacturing stage will be the same you have observed at a smaller scale.

What you want is that the evolution of product time, temperature versus time and the drying duration are the same in the two freeze-dryer. Actually, MicroFD gives you some interesting possibility for minimizing the effort needed to transfer a process, as I will show you in a while.

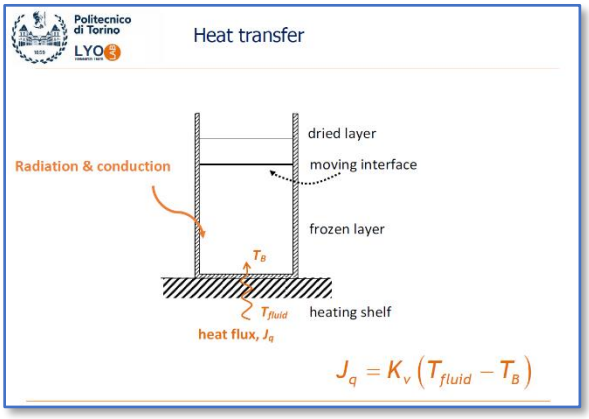


At first, we have to understand why we have a problem of process of scale up, of process transfer. The problem is related to the way heat is transferred to the batch. In a freeze-drying process we supply heat to the product, and this heat is used for ice sublimation. So, the product is something like a closed system in which we introduce heat and we remove it through sublimation. If the rate of heat supply is equal to the rate of heat removal, then we are in a sort of equilibrium. If the rate of heat supply is higher than the rate of heat removal, then we are giving to the product too much heat. And the result is that the temperature increases and may overcome the limit temperature.

So, the heat transfer to the batch is key point that has to be considered. This way, we focus on the paper published by Bernadette Scutellà five years ago, more or less, on applied thermal engineering. They investigated the heat flow rate in the so-called central vials, so vials in the central position of the batch, and the heat flow rate in the edge vials. Distinguishing between edge vial C, vials that are in contact with the rail, with the metallic frame used for loading and unloading process, and edge vial E, that are the edge vials not in contact with the metallic frame.

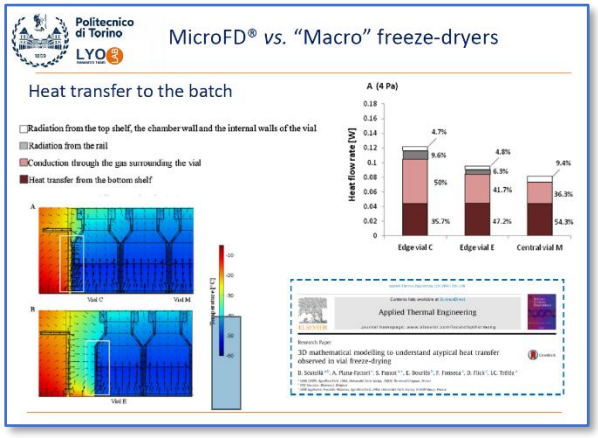
If we have a look at the graph on the right hand side, we may see that, at first, there is a different heat flow rate according to the position of the vial in the shelf. Vial in the central position, we see it's a lower amount of heat with respect to vial at the edge of the shelf, first of all. Second, vials receive heat from the shelf, they receive heat through conduction in the gases surrounding the vials. They receive heat due to radiation from the rail, from radiation from the top shelf, or from chamber walls. Obviously, the heat transfer from the shelf is ... well, it's the same. It's not dependent on the position. Which is dependent on the position is the heat related to radiation, the heat related to conduction.

Okay. Usually, when people deal with the heat transfer mechanism, the rate of heat transfer to product in freeze-dryer, usually people do not consider the heat flow rate. They consider another parameter that is the famous Kv, the heat transfer coefficient. Let me introduce this parameter. This is a sketch of what is occurring in the vial in a freeze-dryer. In the vial, we have a first layer, dried layer, moving interface from the top to the bottom of the product. We have heat flux, from the bottom or from the shelf. Heat transfer due to radiation, conduction and so on. All the heat transfer mechanisms that were evidenced by Bernadette in her paper.



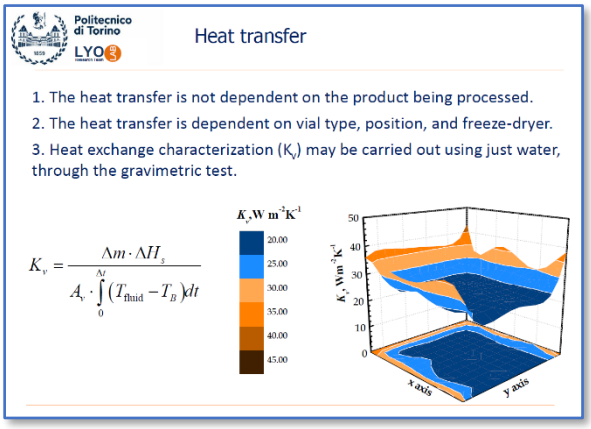
Actually, people uses always this equation. This equation, we say that all the heat transfer to the product is given, is written, is calculated, is expressed as a product. A product by the difference between the temperature of the heating fluid and the temperature of the product at the bottom of the vial. This is called the driving force. And this driving force is multiplied by the overall heat transfer coefficient.

Obviously, if we look at or we focus on the edge vials or on the central vials, the difference Tfluid minus TB is more or less the same. But as Jq, as the heat flux in the product is different, then the result is that Kv is different. Kv for edge vials is different with respect to Kv of central vials. So usually people, instead of using this kind of representation so clearly expressing the heat flow rate, usually people in freeze-drying domain talk about Kv.



They are basically the same, because Kv is multiplied by this difference, the fluid usually known, TB may be measured quite easily. And so from Kv, you may get the value of the heat flux. But it is important, because we will talk about Kv in the different unit, MicroFD and the larger scale apparatus.

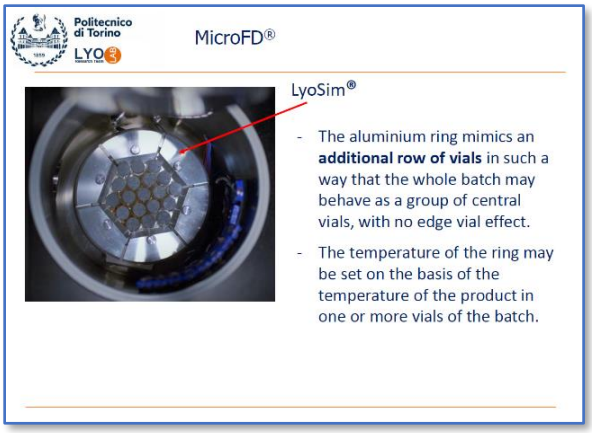
First point. The heat transfer is not dependent on the product being processed. Talking about heat transfer, we're talking about the radiation from the rail, radiation from chamber walls, convection in the gas, about the heating fluid. Okay? We are not talking about the product inside the vial. We may carry out experiments with water, with water and sugar, with water and active pharmaceutical ingredient. But if we are investigating the rate of heat transfer, so Kv, the value of Kv is not dependent at all on the product being processed. First important concept.



Second. Heat transfer is dependent, obviously, in vial type, on vial position, on the freeze-dryer. Because all this element affects the rate of heat transfer to the product. And if you want to get the value of Kv, the only way you have to get it, to take picture of your experiment, is to carry out the so-called gravimetric test. You run a cycle in sublimation test for three hours, four hours, five hours, something like that. And you measure the weight loss, delta m, in all vials. You multiply this delta m by the entity of sublimation. You divide this product by the area of your vial, and by the temperature difference.

So you need to measure not just the weight loss, but also the temperature in some vials. But this way, you get Kv, and you get a detailed picture of Kv in your batch. Like the one shown in the right hand side of this slide, with higher value of Kv at the edges of the shelf, and lower value in the central part. What about MicroFD? This is what you may get in your pilot scale unit, or even in an industrial scale unit, by running one test with just water. You don't need any active pharmaceutical ingredient to carry out this test.

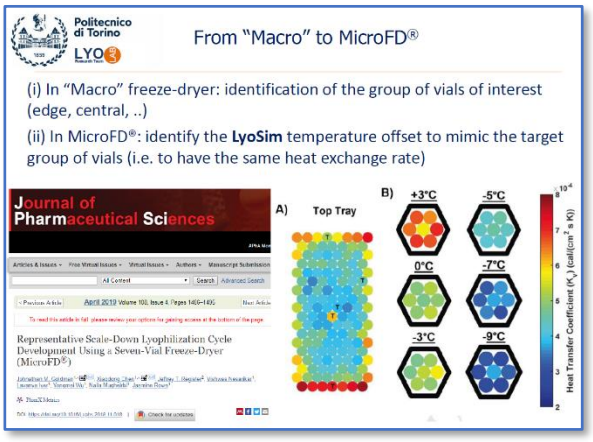
In MicroFD, the situation is slightly different, because in MicroFD, you have your batch of vials, 19, 7, it depends on the size of these vials. And the vials are surrounded by an aluminum ring. The temperature of this aluminum ring may be manipulated. You may independently on the temperature of the heating shelf. I mean, you may set the temperature of this ring to be equal to the temperature of the heating shelf, or to a different value. There is the possibility to select what is called offset. I mean, you measure the temperature in some vials of the batch, put in thermocouples inside. And the temperature of this aluminum ring is set on the basis of the temperature of the product. So it's given by the temperature of the product, plus minus the offset. It depends if you have selected a positive offset, or a negative offset.



This is an important degree of freedom that you have. Why? Because by manipulating the temperature of the aluminum ring, you manipulate, you effect the amount of heat that is given by the equipment to the vials that you are processing in MicroFD. And by this way, you may replicate, you may reproduce what? Well, in principle, the aluminum ring may reproduce, may replicate a row of vial. In this way, if you set properly the temperature of the aluminum ring, the dynamics that you are investigating in MicroFD will be the dynamics of the vials in central position in the larger scale equipment. This is useful for what reason?

Well, first, obviously, central vials. The so-called central vials represent the majority of the vials of a batch. The drying time is related to the velocity of drying in the central vials. But in principle, you may tune in a different way the ring temperature to heat more the vials in this batch, to replicate in MicroFD, the dynamics of the edge vials of your larger scale unit. This is important, why? Well, because obviously, edge vials are characterized by the higher temperature. So if you want to be sure that no collapse, no shrinkage occurs in your large unit, this type of study is what you have to do.

So if you want to move from Macro freeze-dryer, just a unit, to MicroFD, what you need to do? At first, you need to identify in the larger scale unit, the group of vials of interest, at first. You want to investigate what will occur in central vials, because you are interested in evaluating dry length, duration, you are focusing on the majority of the batch, and so on. Or you are interested in the edge vials, because they are the [inaudible 00:23:07] in your batch. This is the first point.



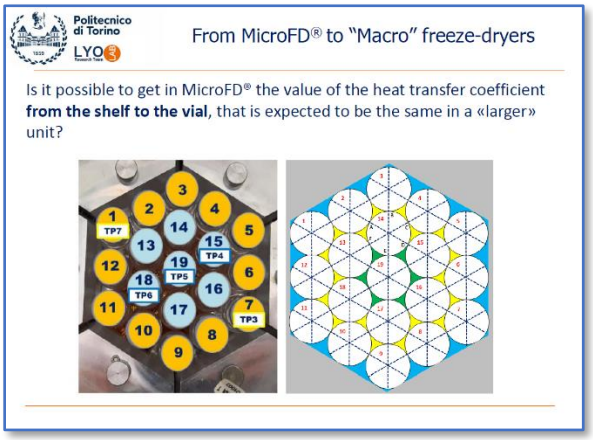
And you need to carry out the characterization, the gravimetric test in the larger scale unit. But it's a test that you carry out once in your life with the specific type of vials that you will use. It's a gravimetric test. It last a few hours. It just need water, water for injection, and no more than this. Then you move to MicroFD, descends from Macro to MicroFD. And in MicroFD, you need to identify which is the LyoSim temperature offset to mimic the target group of vials, to have the same heat exchange rate.

This is a paper published by Goldman three years ago, more or less. In graph A, you see a color map showing the value of Kv in a larger unit. In B, you may see color map Kv values obtained in MicroFD, modifying just the temperature of the ring. What you see? You may see that if you select an offset of plus three, in your MicroFD, you replicate the heating condition of the first vials. If you select a LyoSim temperature of minus five, you replicate in your MicroFD the evolution of the product in the central vials. This is just dependent on the heat transfer rate. It does not depend at all on the formulation being processed.

So you may carry out this test once in the lab, using water for injection, distilled water, in your vials. You get this infos, and then you may use this infos. So you select the temperature offset, and you will be sure that your MicroFD will behave like the central vials of a larger unit, or like the external vials of the

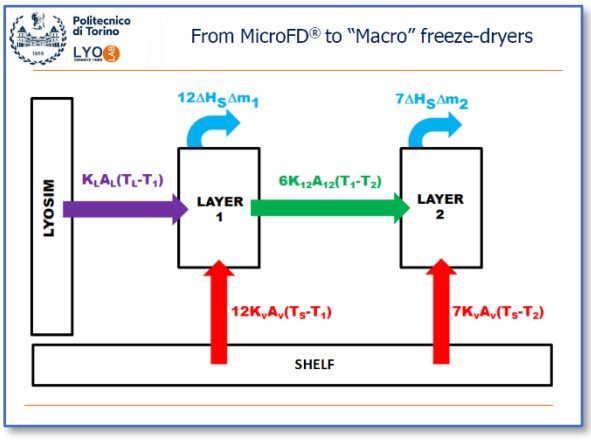
larger unit. So beside providing significant time saving and raw material saving, it gives you the flexibility to replicate this type of dynamic.

But you have also another possibility. You may, in that previous slide, I was talking about moving from larger scale unit to a smaller one. So I want to replicate Micro, what will occur in a larger apparatus. You can use a different approach. I mean, I carry out a test in MicroFD without paying attention to the temperature LyoSim. I want to save time, from this point of view. I don't want to carry out this characterization and so on. So just one test. And I want to use the result I will get for process scale up, for process transfer. Is it possible to do this or not? Well, let's see an example.



Here is a picture of a MicroFD that is in my lab. 19 vials in its configuration, 10R. And in the right hand side, you find a sketch of this batch. Why I'm showing you this sketch? Because it's quite meaningful, I mean. If you have a look at vial 19, the vial in the center of the batch, this vial surrounded by six other vials. If you have a look at vials numbered 13, 14, 15, 16, 17, 18 ... I stop with 18. You have that all these six vials are, again, surrounded by other six vials. So these seven vials in the second part of the batch receive heat from the bottom and receive heat from six vials surrounding them.

This equation is a little bit different from the external vials, the vials in contact with the LyoSim. Because in this case, each vial is surrounded by three or four vials, is in contact with LyoSim. So, this situation is a little bit different. But then we make some modeling of this system. So, we may group central vials into what is called in this guide, as layer two, the other vials in the layer one. Vials in layer two received heat from the shelf, from the other vials of the batch. And there is heat leaving these vials, related to ice sublimation.



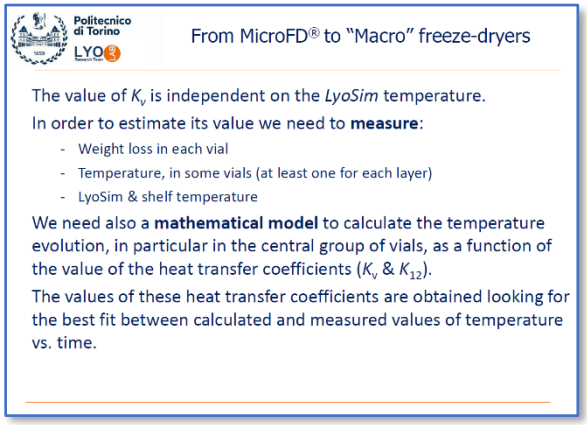
If we focus on layer one, vials of layer one receives heat from the shelf, exchanges heat with layer two and with the LyoSim. And they lose heat due to sublimation. Here you had seven and the 12, because there are seven vials in your layer two, and 12 vials in layer one, so it is curing in one vials and has to be multiplied by seven or by 12 to account for this.

The key point is that the Kv coefficient expressing, describing the heat transfer from the shelf to the vial in the layer, in the freeze-dryer, is the same for layer one and layer two. It's the same of the paper of Bernadette Scutellà, in which the heat flow rate from the shelf was always the same, it depended on the

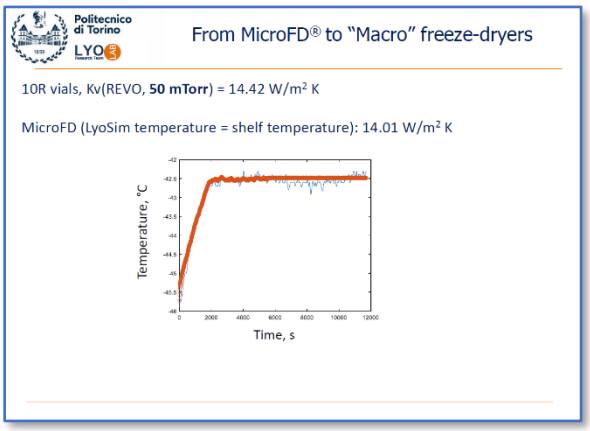
position of the vial over the shelf. And it also is independent on the dryer size, on the dryer characteristics. It is always the same Kv.

K12, I mean, the heat transfer coefficient due to vial-to-vial contact. Also, this is the same for all vials of layer two, and Is expected to be the same even in a larger scale unit. What is different is KL, in this case. So what kind of test you need to carry out? Well, in principle, if you have in mind this picture, what you have to think is this. I carry out a test, I measure the weight loss in all the 19 vials. It takes a few minutes measuring this weight loss in all the vials. I measure the temperature of the shelf, yes, and the temperature of a few vials in group one and in group two, T1 and T2. TL is obviously known, is the temperature of LyoSim.

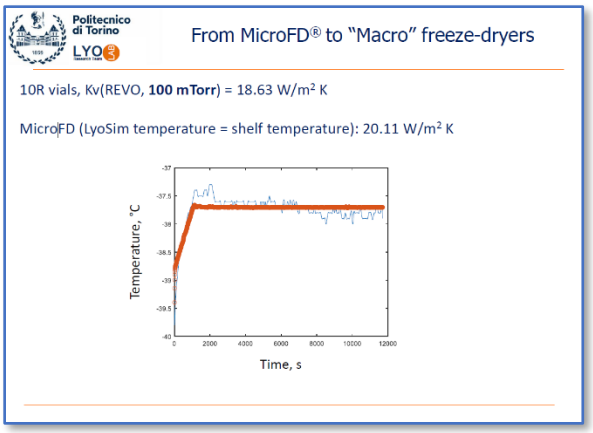
So I get a series of variables that are measured. And I may use this measure variable to estimate the value of Kv, K12 and KL. It's something similar to what ... I don't know if you have ever carried the pressurized test, or you have any experience with pressurized test, MTM, with this type of software and of our equipment. In that case, pressurize is force in the machine. Then, there is a mathematical model with some unknown parameters. And the values of these parameters is estimated, looking for best fit between calculated and measured values of pressurized.



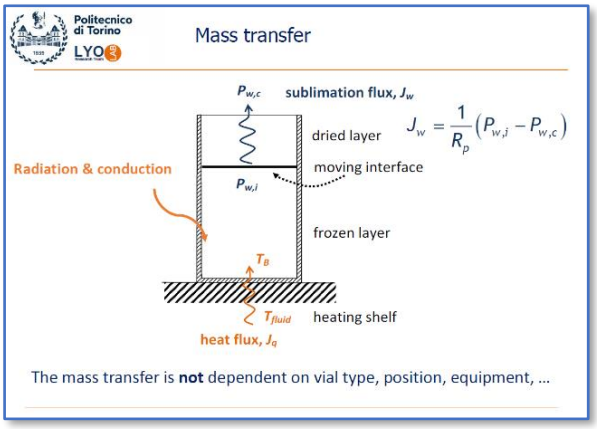
Here is exactly the same. Here, we measure the temperature in the vial with a mathematical model used to calculate the temperature evolution, and the software that looks for the best value of Kv, K12, in order to get this best fit. Here, we see an example of results. 10R vials, processed in REVO this vial, vial scale unit. 14.4 is the value of Kv. I carry out the test in MicroFD, without paying attention to LyoSim temperature. I set it equal to shelf temperature. No problem at all. I measure the temperature, measure the weight loss. I use a model. I'm not giving some case about that, because they are not easy. But anyways, software, black box. And I look for the value of Kv that provides best value between calculated and measured value of temperature.



The agreement is shown in this graph. The value of Kv I obtain is very close to the value obtained in REVO. Here is an example of results at 100 mTorr chamber pressure, a different one, also the scales. Very good agreement between modeling and measurement, and satisfactory agreement with respect to Kv. So I have the possibility, if I focus on heat transfer, to use MicroFD in two way. From Macro freeze-dryer to MicroFD, I use information obtained in the larger scale unit to replicate in MicroFD the target group of vials. And so I may develop my process taking into account what the product will experience in the different unit. Or I may carry out a gravimetric test, again, in MicroFD without paying too much attention to LyoSim temperature. And I may use this results moving for scale up process. I estimate in MicroFD, the value of Kv that will be obtained in the larger part.

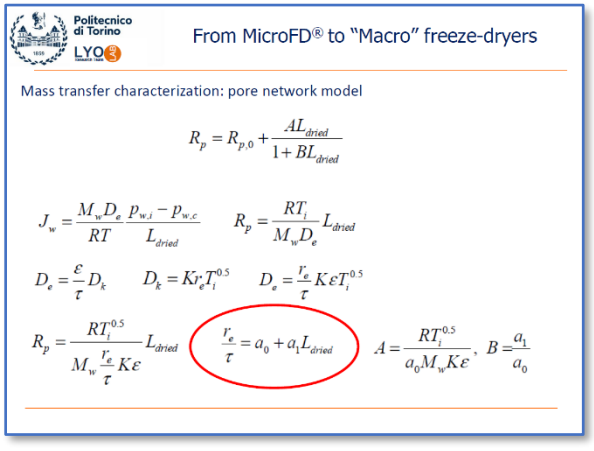


What about mass transfer? With respect to mass transfer, we have, again, to focus on the equation that is used to describe this mass transfer. The equation, that you probably know is the one I'm showing to you. I mean, the mass flux from the vial, the chamber, is again, given by a product. A product between a parameter, in this case, Rp, so called resistance of the product, and the driving force. Driving force here is the difference water vapor partial pressure at the interface of sublimation and in the chamber.



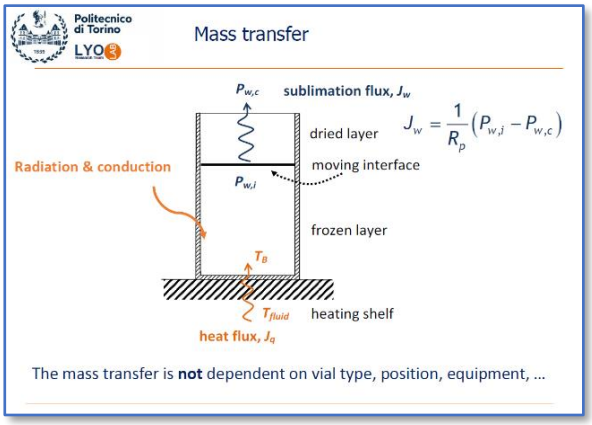
Also in this case, this driving force is known. Water vapor partial pressure in the chamber is equal to chamber pressure, for sure. And water vapor partial pressure in the interface of sublimation is a well known function of product temperature. So this driving force is known like Tfluid minus TB in Jq equation. So if we know Rp, we are able to characterize mass transfer from formulation to [inaudible 00:35:35]. Key point is that mass transfer is not dependent on vial type, vial position. Only equipment. Provided that the same freezing path is used.

Rp, you probably have seen this equation that have the parameters A, B, and a third parameters, Rp.0. in which way I can use MicroFD to get this parameter? Well, in this case, the story is a little bit more complex, from a theoretical point of view. But then for point of view of the calculations that we did, it's very simple. So I hope, even if we are closer



to the end of this webinar, you may still follow me in this few equation. Unfortunately, I'm an engineer, and sometimes an equation should appear in my presentations. But they are very, very few.

The starting point is that the equation, this one, expressing that the sublimation flow rate actually is the equation used in freeze-drying domain. Everybody freeze-drying talks about Rp. But actually, is a particular version for freeze-drying practitioners of a more general law, that is the Fick's law, the law of Fick. According to the Fick's law, sublimation, the water vapor flow rate is determined this way. Molecular weight of water, effective diffusivity, ideal gas constant, temperature, driving force, and the thickness of the dried layer.



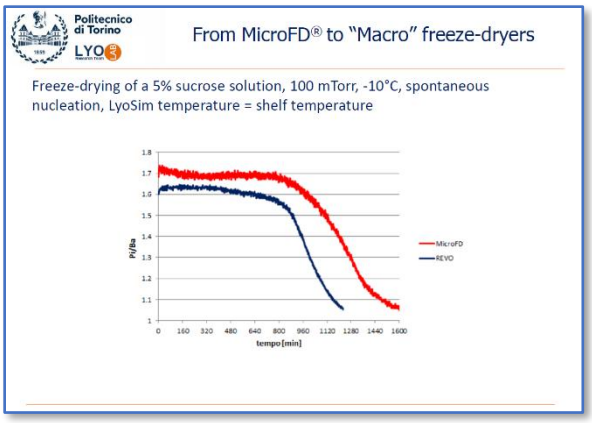
This equation and this one are actually the same, provided the Rp is written in this way. So Rp is actually not just Rp.0 A, B. Okay, but Rp is very specific theoretical background, is ideal gas constant, by temperature, divided by molecular weight, effective diffusivity and thickness of the dried layer. Effective diffusivity is given by the Knudsen diffusivity, multiplied by K porosity, divided by K [inaudible 00:38:55] tortuosity. And Knudsen diffusivity is a function of the mean pore size, re, and of temperature at the power of 0.5.

So if we will place Dk in the equation expressing the effective diffusivity, we get this. And then we will place these into the previous equation expressing Rp, and you get this complex, quite strange equation. A complex equation, there is still one step that has to be done. What about pore size and tortuosity? Usually, pore size and tortuosity are written as a function of layer thickness in this way, with the tau parameter, a0 and a1. If we replace a's re divided by tau, into this equation, we get something, it equal to the A by Ldried divided by one plus BL dried, where A and B are written in this way. So we may express Rp, so the resistance of the K, either using A and B, or using a0 and a1.

But then I'm noticing, I mean, a0 and a1 are two parameters related to the structure of your product. A and B are two fit parameters that are related to the structure of your product, a0 and a1, but also to the temperature of your product. Even if at the power of 0.5, but they are dependent on that. Okay. So a0 and a1 are the two parameters that are independent on the equipment on the thermal history of your product, not A and B. So you can be able to test in your MicroFD. You get Rp versus Ldried. There is a nice software that provides immediately this result.

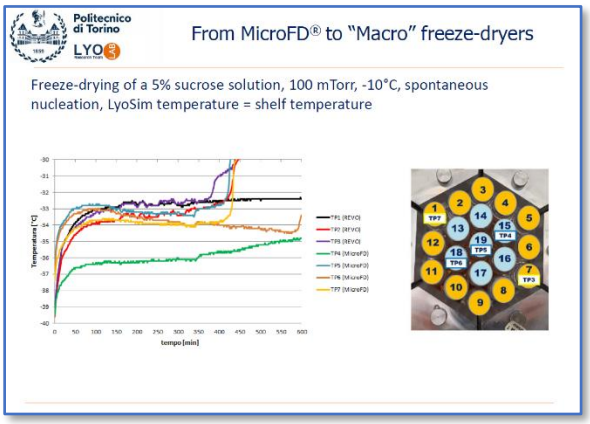
From Rp versus Ldried, you have to extract this information. You get A and B by means of fitting. And from A and B, you get a0 and a1. These two parameters may be used for process transfer. Let me show

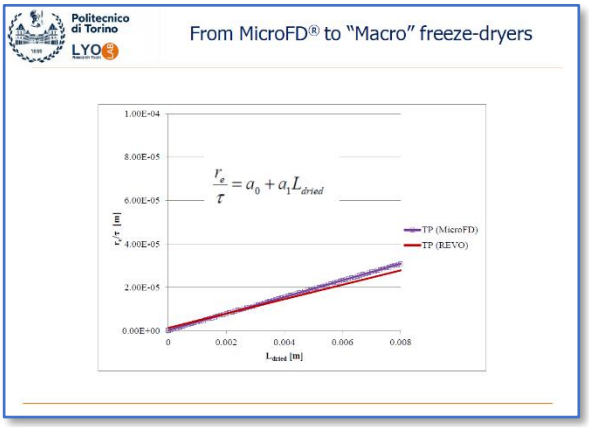
you an example. Here, I was carrying out a very simple cycle, 5% sucrose solution, 100 mTorr, -10 celsius, spontaneous nucleation, in REVO pilot scale unit, and in MicroFD. MicroFD, I was not, at that time, concerned about the temperature of LyoSim. I said, "Okay, temperature of LyoSim is equal to shelf temperature, and let's go on."



Obviously, if I look at the Pirani over barye pressure ratio versus time, I may see that what is occurring in MicroFD is different from what is occurring in REVO. Drying time is different. Drying time is, what? The inflection point of this curve, or in some cases, considered to be the onset or the offset where there ... for sure, the offset, I mean ... when the difference between the Pirani and barye pressure is very small, you may say the drying is ending.

And you may see that in this case, in MicroFD, drying is older than in REVO. So in which way can I transfer the result that came in Micro to the other apparatus? Well, in the test that you have for temperature measurement, and that here you may see temperature measurement in REVO and temperature measurement in MicroFD. And they are different, because I was not concerned about replicating in MicroFD the dynamics of the larger unit. Here, the point of view is from Micro to macro. Okay, you may see, no cases are below -32, no collapse and no shrinkage at all, and so on. And here is the result, the cake structure. Here is the trend of re over tau, so parameters a0 and a1, I obtained in MicroFD and in REVO. They are almost coincident.

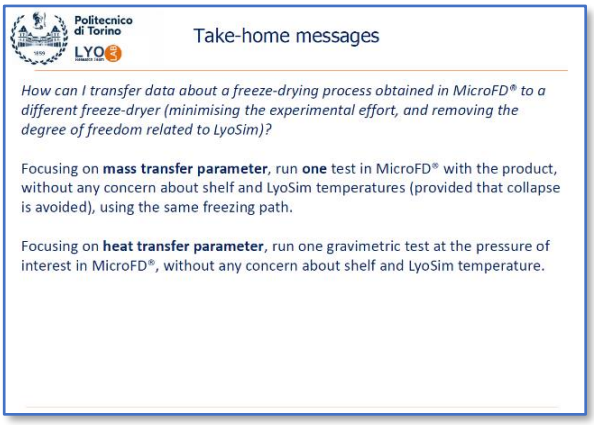




The temperature was different, drying time was different. But if I carefully use, I properly use the experimental data, I get something very, very useful.

So, which are the take-home message? The question you probably have is, how can I transfer about a freeze-drying process obtained in MicroFD to a different freeze-dryer? You have two possibility. The first one is the one, probably more established. There are some papers and all that, some papers from my group ... is to replicate in MicroFD the dynamics of the other equipment. MicroFD provides a very high flexibility in this framework. Once you have done your characterization, you may play as you want, with the drier.

But you may do, also, your job in a different way. Some way, a more traditional way. I mean, you carry out your experiment in MicroFD. From one gravimetric test, you may estimate the value of Kv, expressing the heat transfer from the shelf to the product in vials. And from one test with the product, in this case, you may get the parameter, a0 and a1, that describe the structure of your product K, that you want to be the same in the other unit. Because obviously, you want to avoid collapse or shrinkage. So you have these two approaches that may be used effectively for solving in an original, an effective way, the problem or process transfer and scale up in this unit.



In the end, I would like to acknowledge my team at Politecnico di Torino. These are the guys and girls that work in this field recently. It's part of the LYO Lab Research Team, [inaudible 00:46:45] involved in MicroFD, and as well as Millrock Technology and then Pharmatech, Italian branch, because they are currently solving various issues related to the machine. And they fully supported my job and my experiment with the tool. And obviously, I would like to acknowledge all of you for your attention. And I would like also to invite you to ask question, or curiosity about what you have seen in this webinar.

Thank you.