Transfer of a Legacy Product between Two Sites: How to improve Process Robustness by using Mathematical Models

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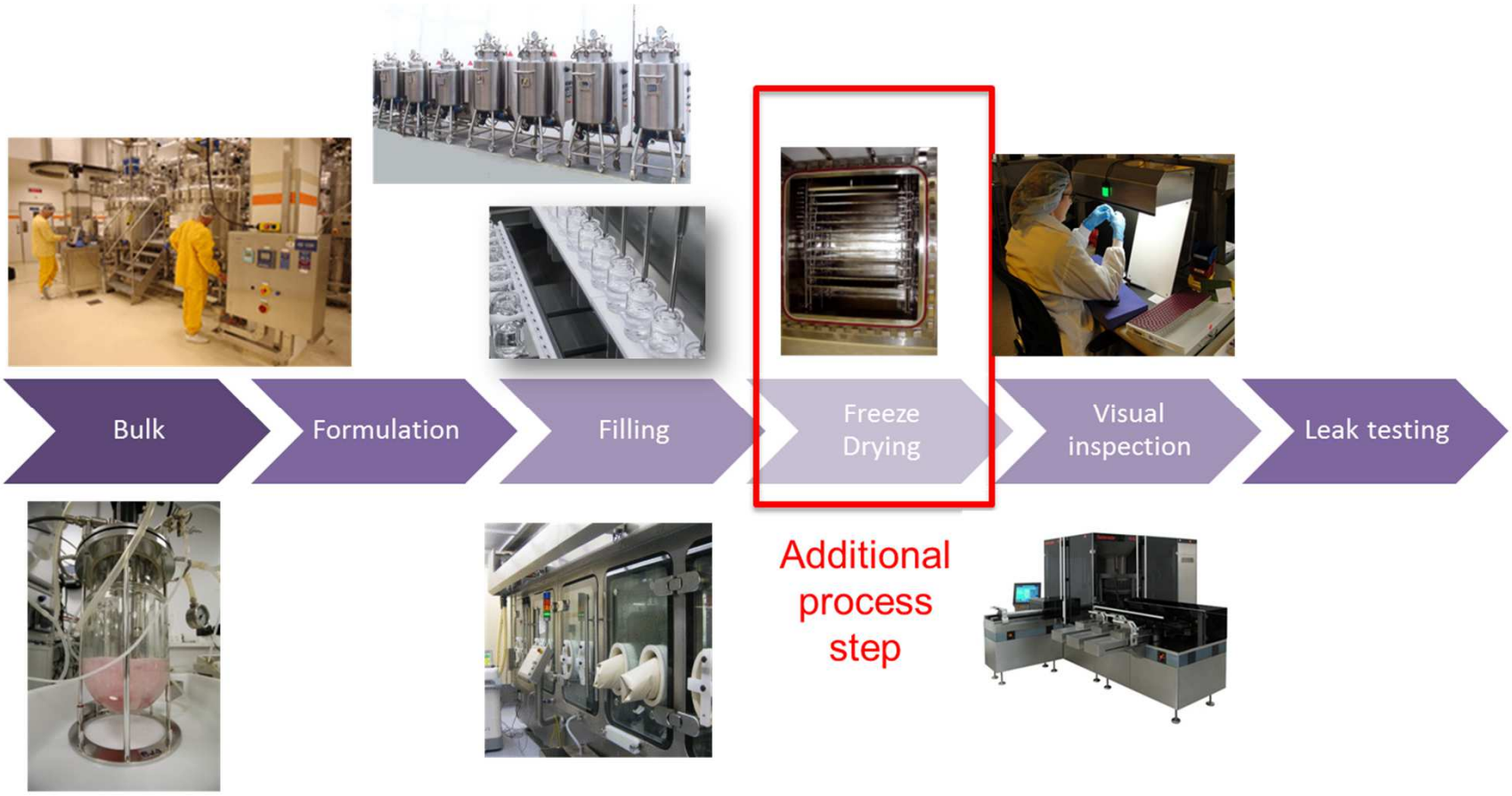
Introduction

Vaccine Process Description



Introduction

Context and situation

➔ Improving the reliability of a freeze drying cycle developed more than 20 years ago, in preparation for transfer of the process to a new manufacturing site

➔ Limited process or physical chemistry data available due to the limitations of technology at the time the product was developed

➔ Formulation characterized by a low critical temperature

Cake aspect variability was observed between batches (edge vial effect) with the original freeze drying cycle

Edge vial defect

Good unit

Introduction

Methodology

➔Formulation

- Before starting the development of the freeze-drying cycle, thermal characterization of the product

➔ Process development

- Historically “flash freezing” was applied before primary drying, is it necessary?
- Characterization of the heat transfer coefficients (Kv) of the different freeze dryers (Manufacturing and pilot)
- Maximum mass flow rates achievable by the equipment at different pressures (choked flow),

➔Simulation

- Thanks to Rp (Product resistance) and Kv, creation of a design space for the freeze drying cycle and determine optimal process parameters.

➔Robustness study at small scale

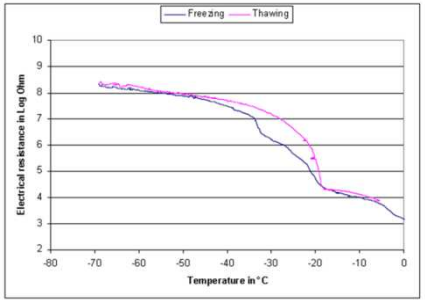
➔Validation at commercial scale

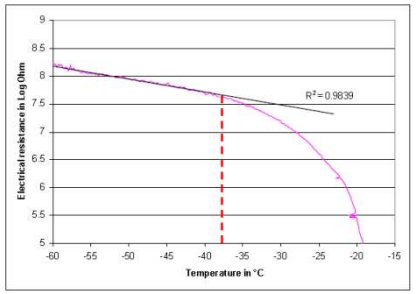
Formulation re-characterisation for freeze drying

Collapse and Glass Transition temperature determination

Initially formulation had been characterized with an Eutectic Monitor (Finn-Aqua Aw2)

Electrical resistance of conductive solutions depends on the temperature. Critical temperature was estimated through a shift in the heating curve





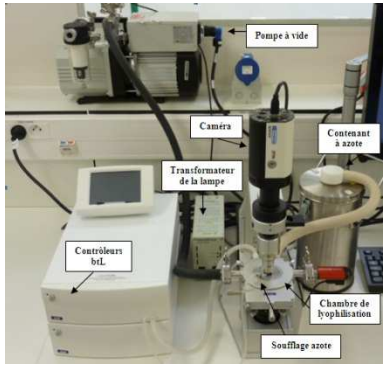
Critical temperature ≈ -38°C

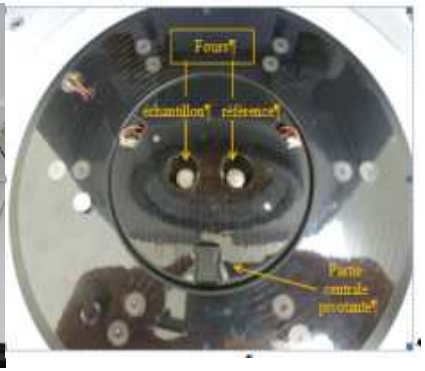
Formulation re-characterisation for freeze drying

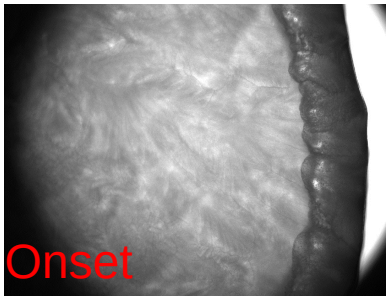
Collapse and Glass Transition temperature determination

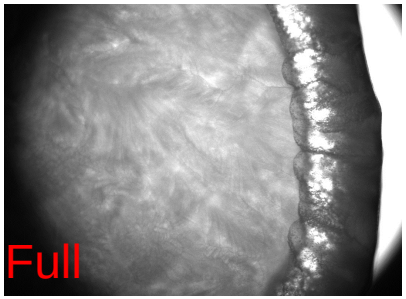
Collapse (Tc) and Glass transition (Tg') temperature measured with a cryomicroscope and DSC.

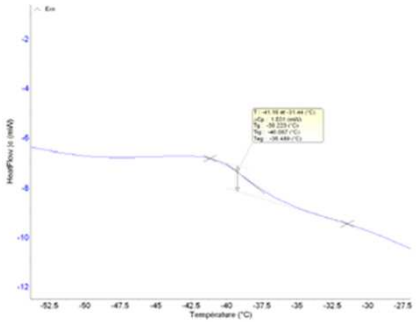
Collapse temperature = appearance of slight white holes on the sublimation front







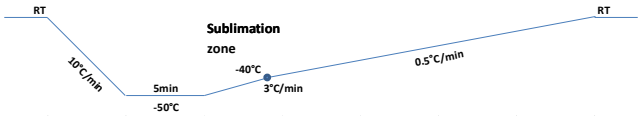


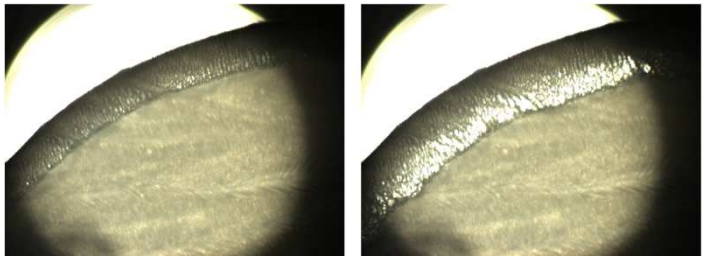


Formulation re-characterisation for freeze drying

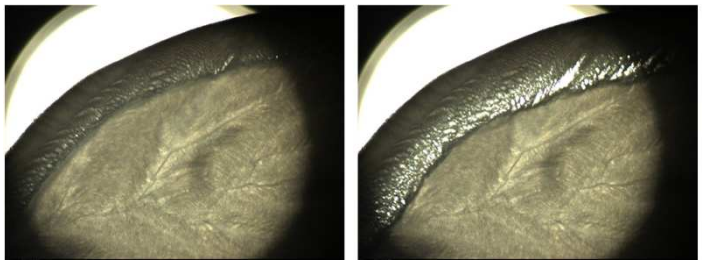
Collapse and Glass Transition temperature determination

The Final Bulk formulation was characterized by a Tc of -38°C and a Tg' of -38.4°C.

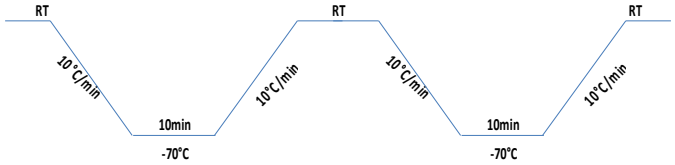


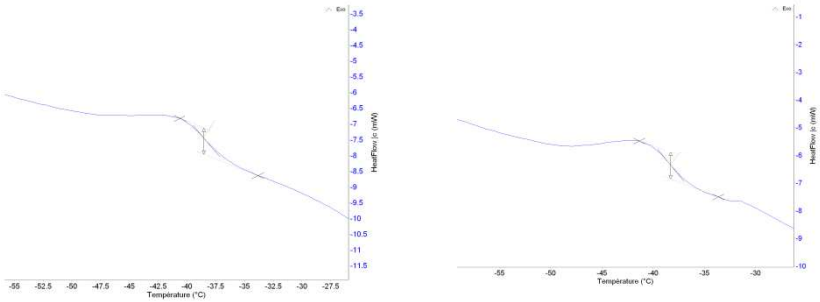


onset collapse-38.1° C **full collapse -37° C**



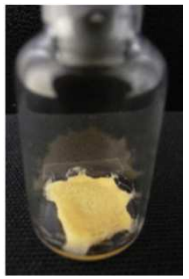
onset collapse-38.2° C **full collapse -37.3° C**





Tc and Tg' are generally considered as critical for the freeze drying process

Product temperature has to be maintained below Tc/Tg' during primary drying in order to avoid processing defects such as collapsed cakes

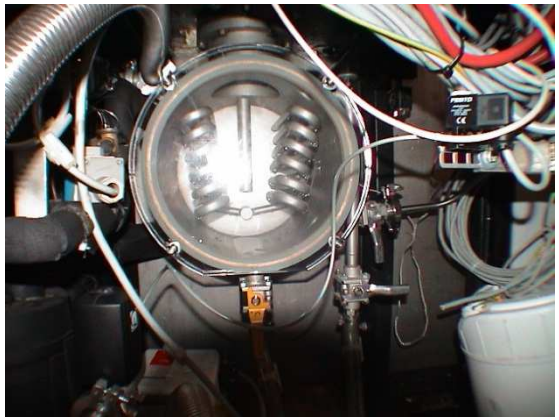


Process development

Evaluation of the impact of the freezing rate on product potency

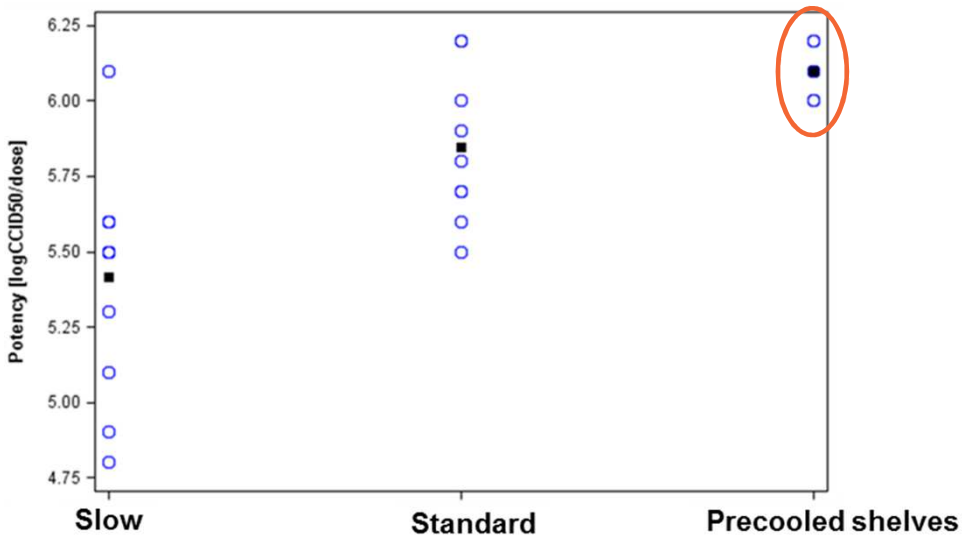
Equipment used:

Lyo GT6 STERIS/ Butterfly Valve



3 freezing protocols tested:

- Slow freezing rate (0,5°C/min)
- Standard freezing rate (2°C/min)
- Fast freezing rate (precooled shelves)



Need to keep “flash freezing” to maintain potency

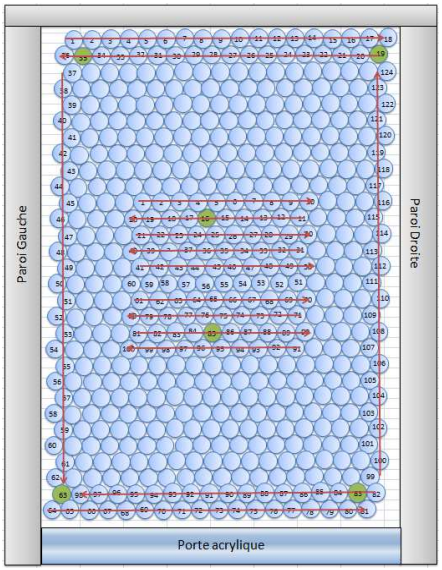
Process development

Characterization of the heat transfer of the pilot and manufacturing freeze-dryers

Pilot Freeze dryer: Vial heat transfer coefficient (Kv) vs Pressure (4, 6, 9, 15, 40, 50 Pa Ts 0 and -40 ° C)

Gravimetric method (center and edge vials) (Pikal et *al*., 1984, 2000, Pisano et *al*., 2011, Hibler et *al*., 2012)

- 2R Filled vials with water (ca. 1,8ml)
- Place temperature probes in selected vials (Tempris probes)
- Carry out freeze-drying cycle until ~ 25-30% of the total mass has been removed
- Evaluate mass flow rate



124 vials weighed at the edge
100 vials weighed in the centre

$$\dot{Q} = \dot{m}\,\Delta H$$

- $\dot{Q}$ [W]: heat flow rate;
- $\dot{m}$ [kg s-1]: mass flow rate;
- ΔH [J kg-1]: heat of sublimation;

$$\dot{Q} = Kv\,A\,(T_s - T_B)$$

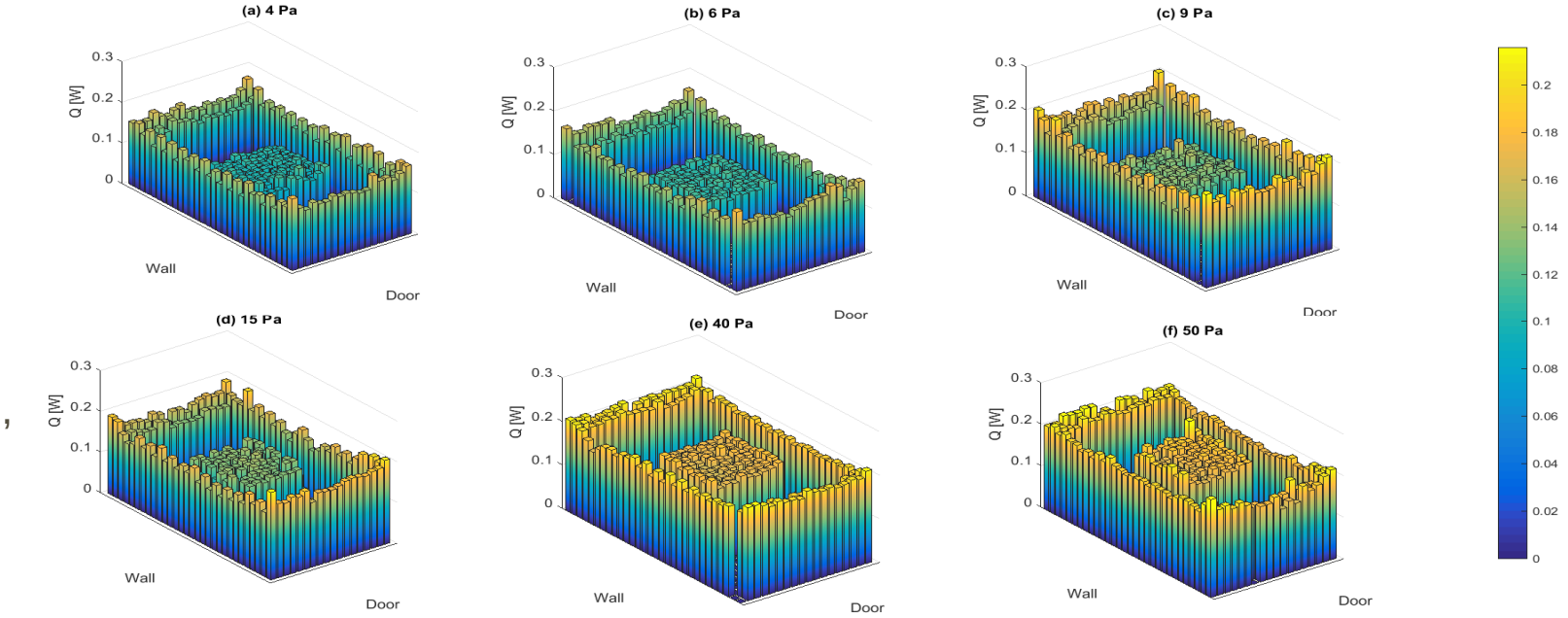
- **Kv [W m^{-2} K^{-1}]= vial heat transfer coefficient;**
- *A* [m^2]: external cross section area of the vial;
- *Ts, Tb* [K]: temperatures of shelf and product.

$$Kv = \frac{\dot{m}\,\Delta H}{A\,(T_s - T_B)}$$

Process development

Characterization of the heat transfer of the pilot and manufacturing freeze-dryers

Pilot Freeze dryer: Heat flow rate within the shelf



Edge vial effect observed at pressures below 15 Pa due to the radiation from the walls to the vials (Rambathla et *al*., 2003), and gas conduction in the drying chamber (Pikal et *al*., 2016, Scutella et *al*., 2017). The higher the chamber pressure, the lower the difference between “centre” and “edge” vials observed the relative contribution of gas conduction in the total heat flux becomes higher at higher pressures.

Rambhatla S, Pikal MJ. Heat and mass transfer scale-up issues during freeze-drying, I: atypical radiation and the edge vial effect. Aaps Pharmscitech. 2003;4(2):22–31.

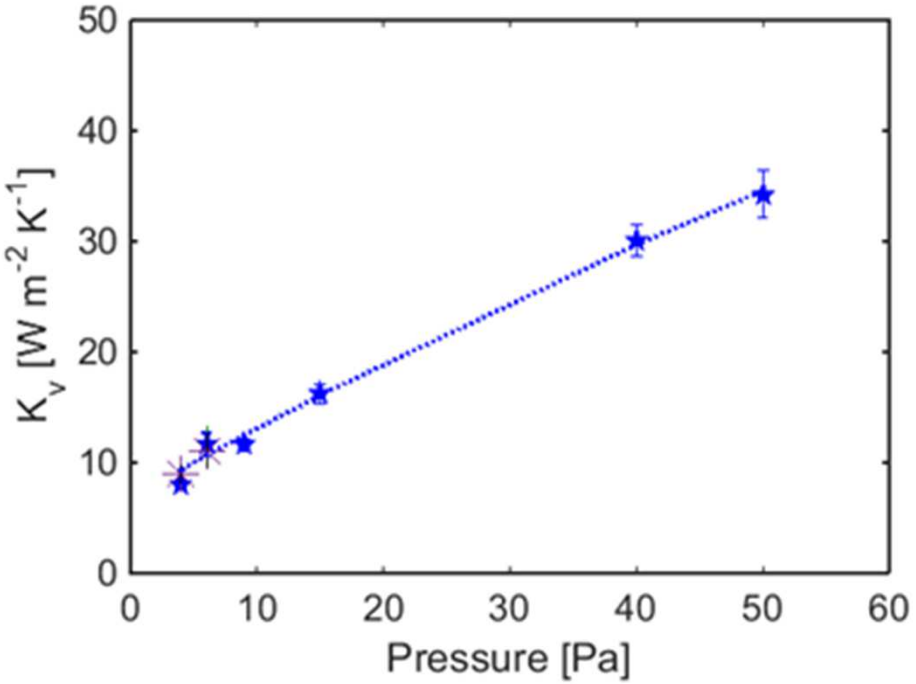
Pikal, M. J., Bogner, R., Mudhivarthi, V., Sharma, P., & Sane, P. (2016). Freeze-drying process development and scale-up: scale-up of edge vial versus center vial heat transfer coefficients, Kv. Journal of pharmaceutical sciences, 105(11), 3333-3343.

Scutellà, B., Plana-Fattori, A., Passot, S., Bourlès, E., Fonseca, F., Flick, D., & Trelea, I. C. (2017). 3D mathematical modelling to understand atypical heat transfer observed in vial freeze-drying. *Applied Thermal Engineering*, *126*, 226-236.

Process development

Characterization of the heat transfer of the pilot and manufacturing freeze-dryers

Pilot Freeze dryer: Vial heat transfer coefficient vs Pressure



,

$K_v = K_c + K_r + K_g$ with

K_c = *heat transfer by conduction from the shelf to the glass*

K_r = *heat transfer by radiation*

K_g = *heat transfer by conduction through the gas*

$$K_v' = C_1 + \frac{C_2 \cdot P_c}{1 + C_3 \cdot P_c}$$

Contact conduction and radiation

Conduction through the gas

Experimental data was fitted with equation described in Pikal et *al*., 1984

Pikal, M. J., Roy, M. L., & Shah, S. (1984). Mass and heat transfer in vial freeze-drying of pharmaceuticals: role of the vial. *Journal of Pharmaceutical Sciences*, Vol. 73, pp. 1224-1237.

Process development

Characterization of the heat transfer of the pilot and manufacturing freeze-dryers

Commercial freeze dryers: Vial heat transfer coefficient vs Pressure

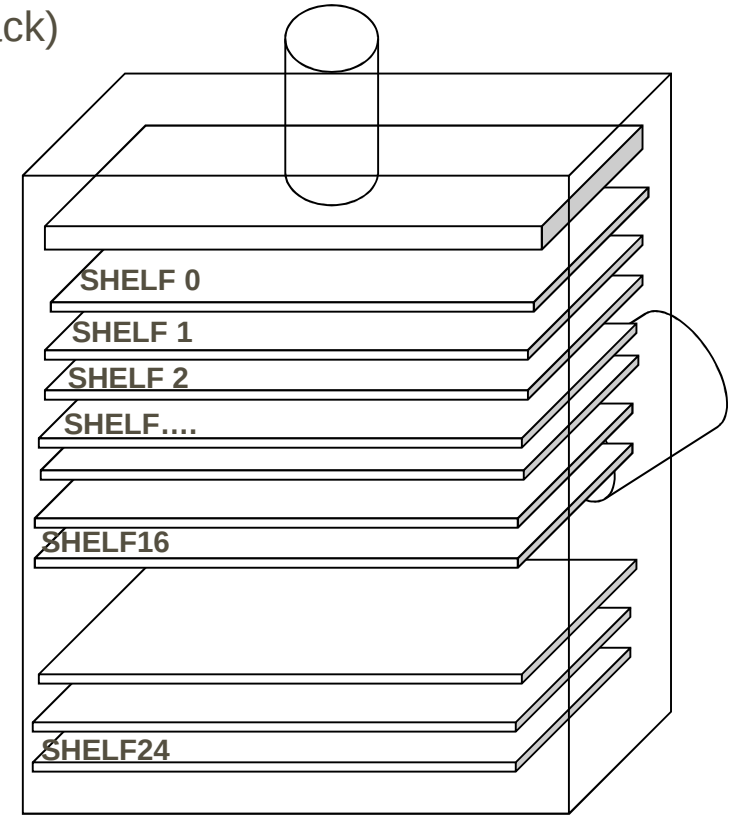
Original Freeze dryer was composed of 24 shelves
Tot shelf surface: 45 m^2
Condenser at the back of the drying chamber

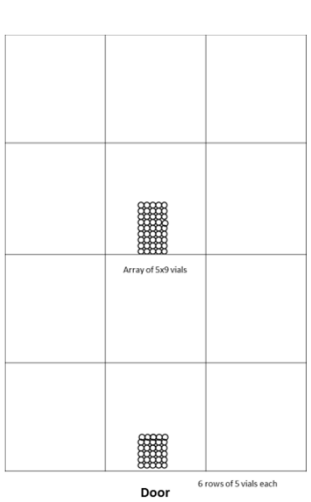
Process development

Characterization of the heat transfer of the pilot and manufacturing freeze-dryers

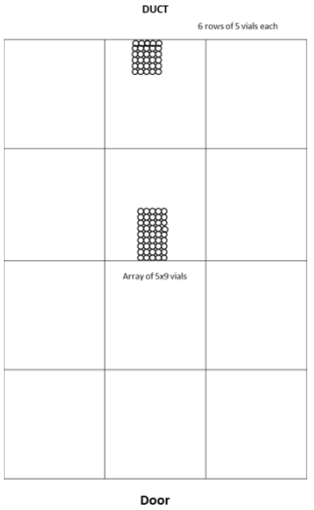
Commercial freeze dryers: Vial heat transfer coefficient vs Pressure

Kv established at 4 and 15 Pa in the Original Manufacturing facility (condenser at the back)

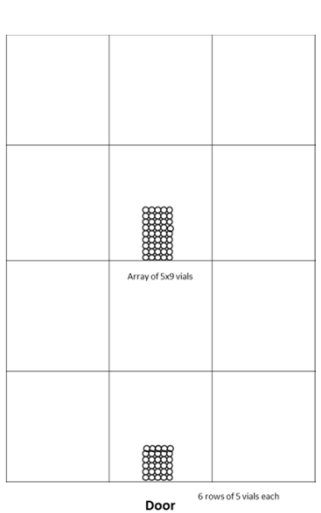




SHELF 1



SHELF16



SHELF24

Same batch of vials used for every trial (pilot and manufacturing)
N = 225 vials

Process development

Characterization of the heat transfer of the pilot and manufacturing freeze-dryers

Commercial freeze dryers: Vial heat transfer coefficient vs Pressure

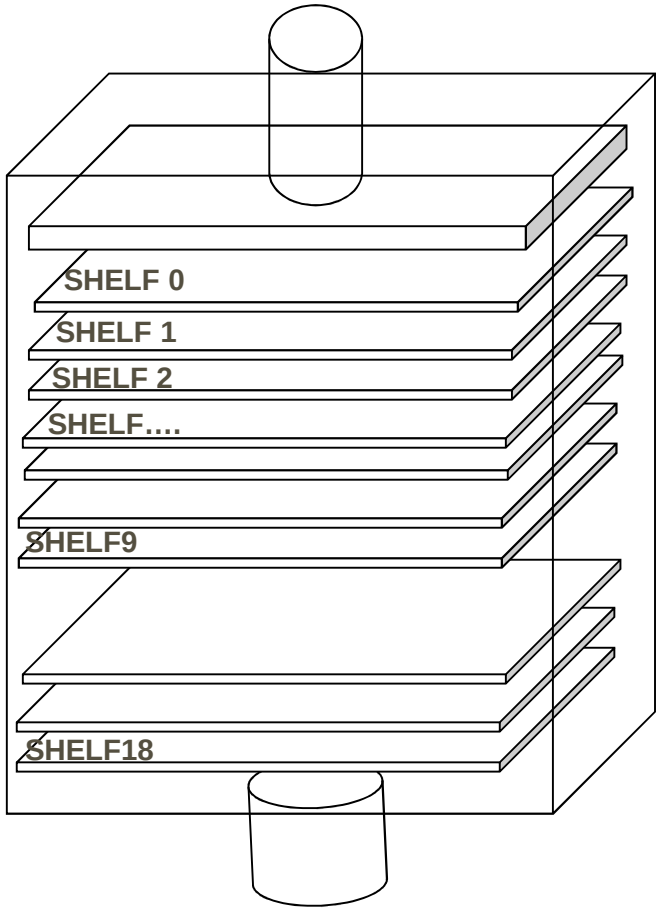
New Freeze dryer was composed of 18 shelves
Tot shelf surface: 52 m²
Condenser at the bottom of the drying chamber

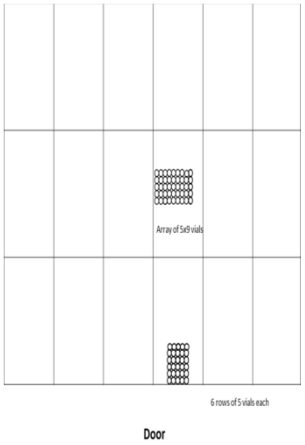
Process development

Characterization of the heat transfer of the pilot and manufacturing freeze-dryers

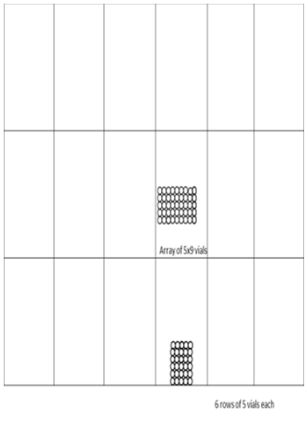
Commercial freeze dryers: Vial heat transfer coefficient vs Pressure

Kv established at 4 and 15 Pa in the new Manufacturing facility (condenser at the bottom)

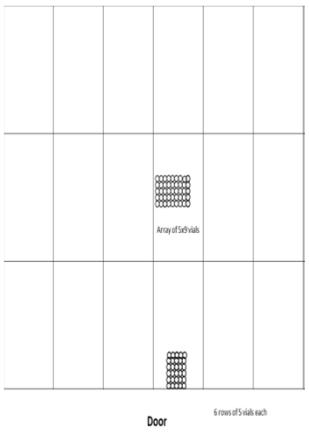




SHELF 1



SHELF9

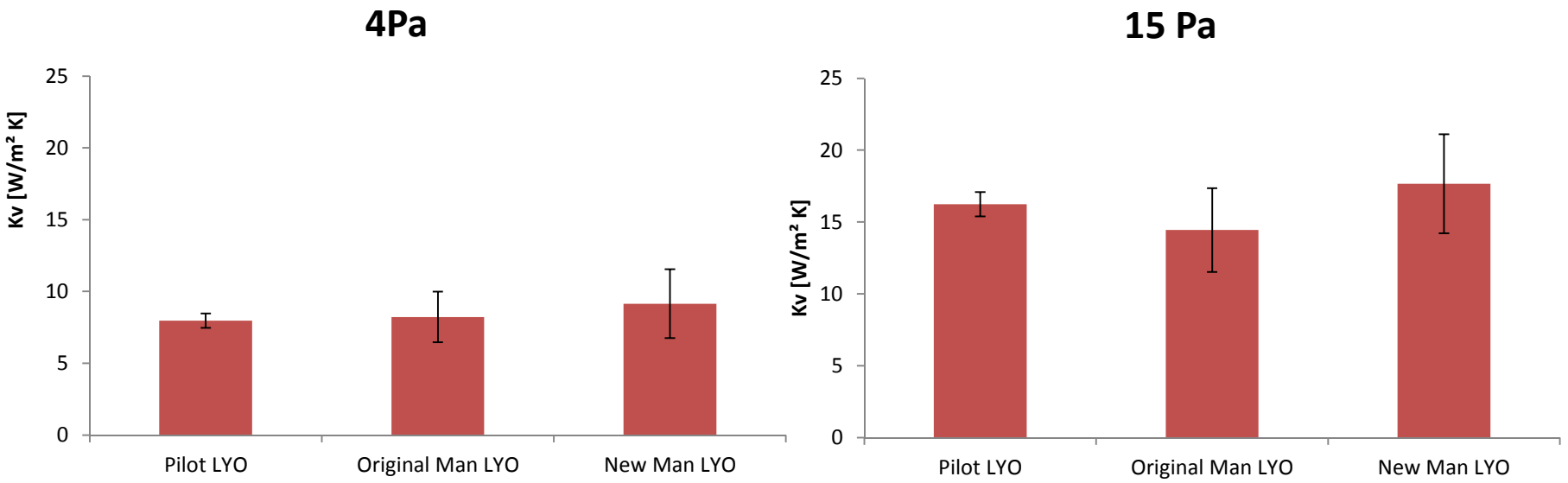


SHELF18

Same batch of vials used for every trial (pilot and manufacturing)
N = 225 vials

Process development

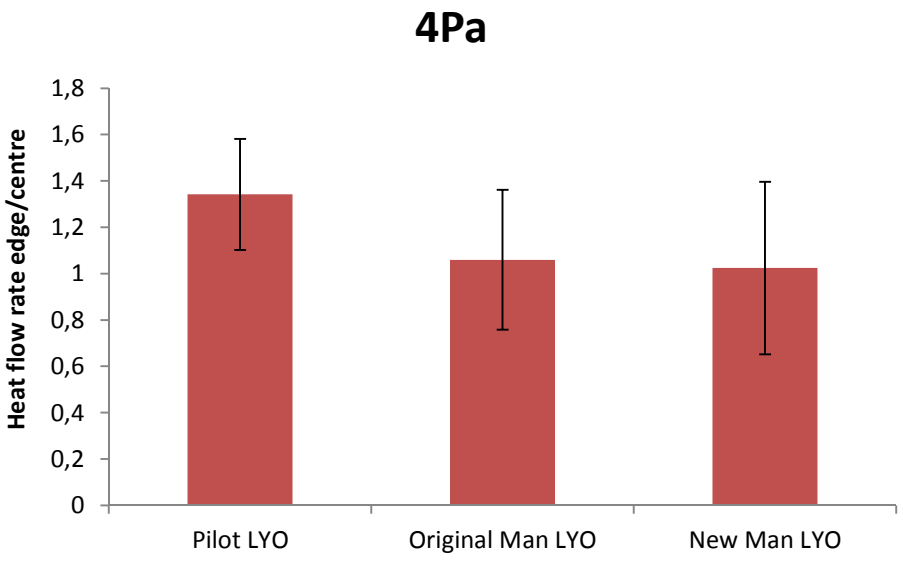
Characterization of the heat transfer of the pilot and manufacturing freeze-dryers

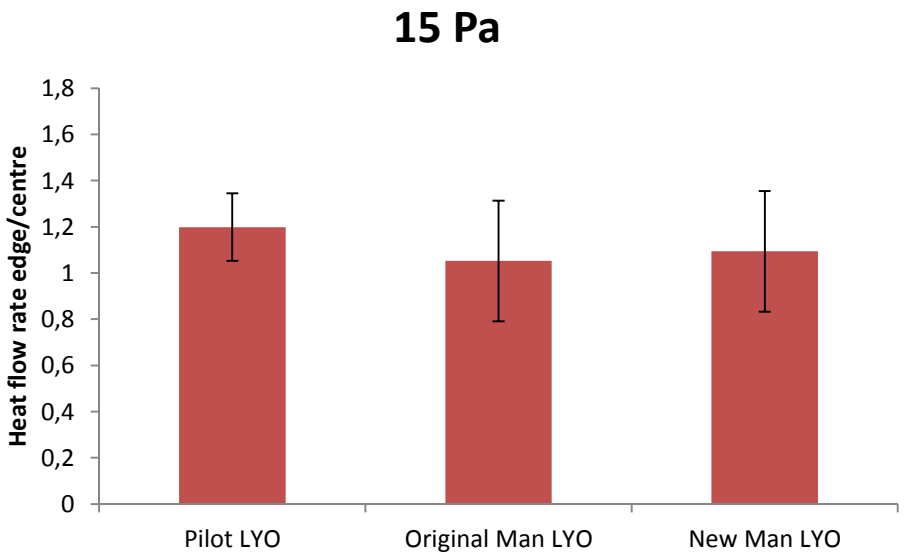


Kv in the same range between pilot and manufacturing Freeze dryers at 4 and 15 Pa for center vials

Process development

Characterization of the heat transfer of the pilot and manufacturing freeze-dryers





Edge vial effect (Heat flow rate edge/center) seems more important in pilot lyo than at commercial scale at 4 Pa (but high SD are visible).
At higher pressure, this difference tends to decrease.

Process development

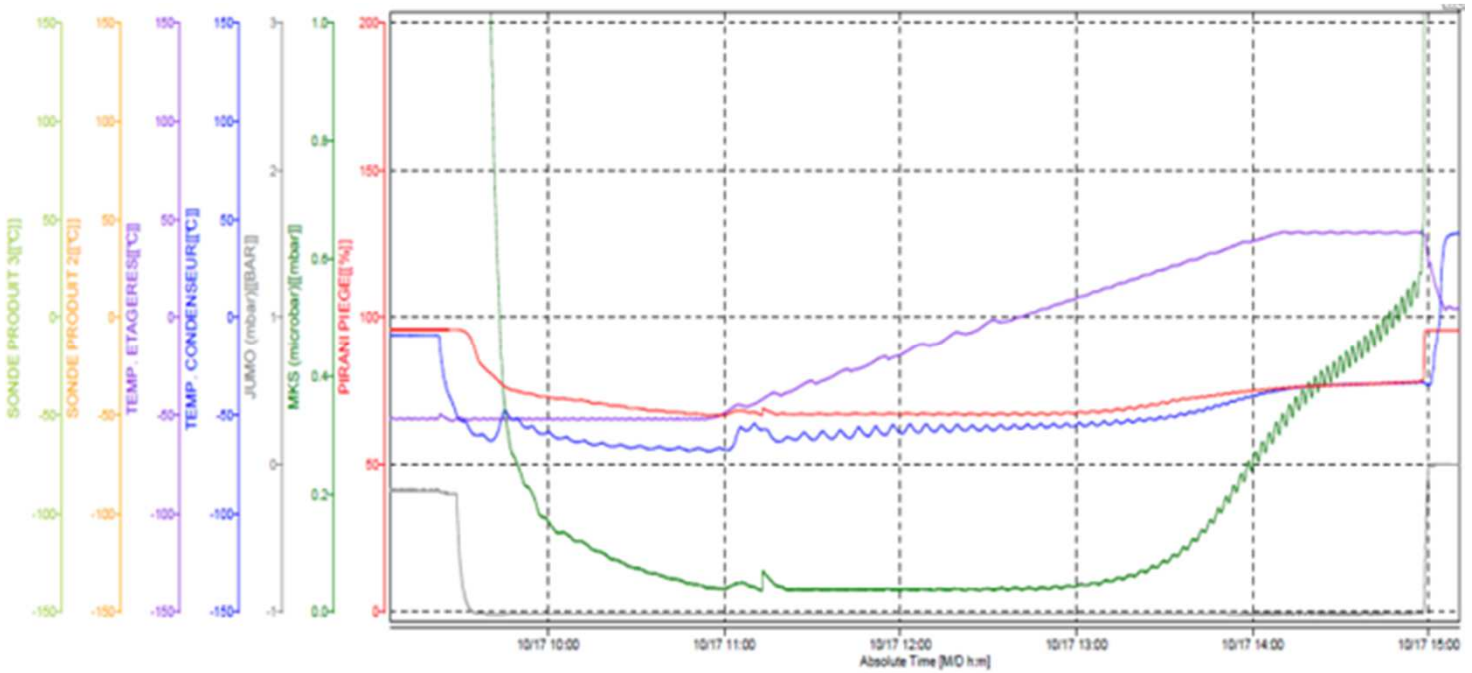
Maximum sublimation rates achievable by pilot and manufacturing freeze-dryers

Procedure described by Searles (2010) was used to achieve this goal

(1) Freeze dryer fully loaded with 2R Vials

(2) Pressure fixed at 4, 6, 9 and 12 pa

(3) Heat the shelves until loss of pressure control

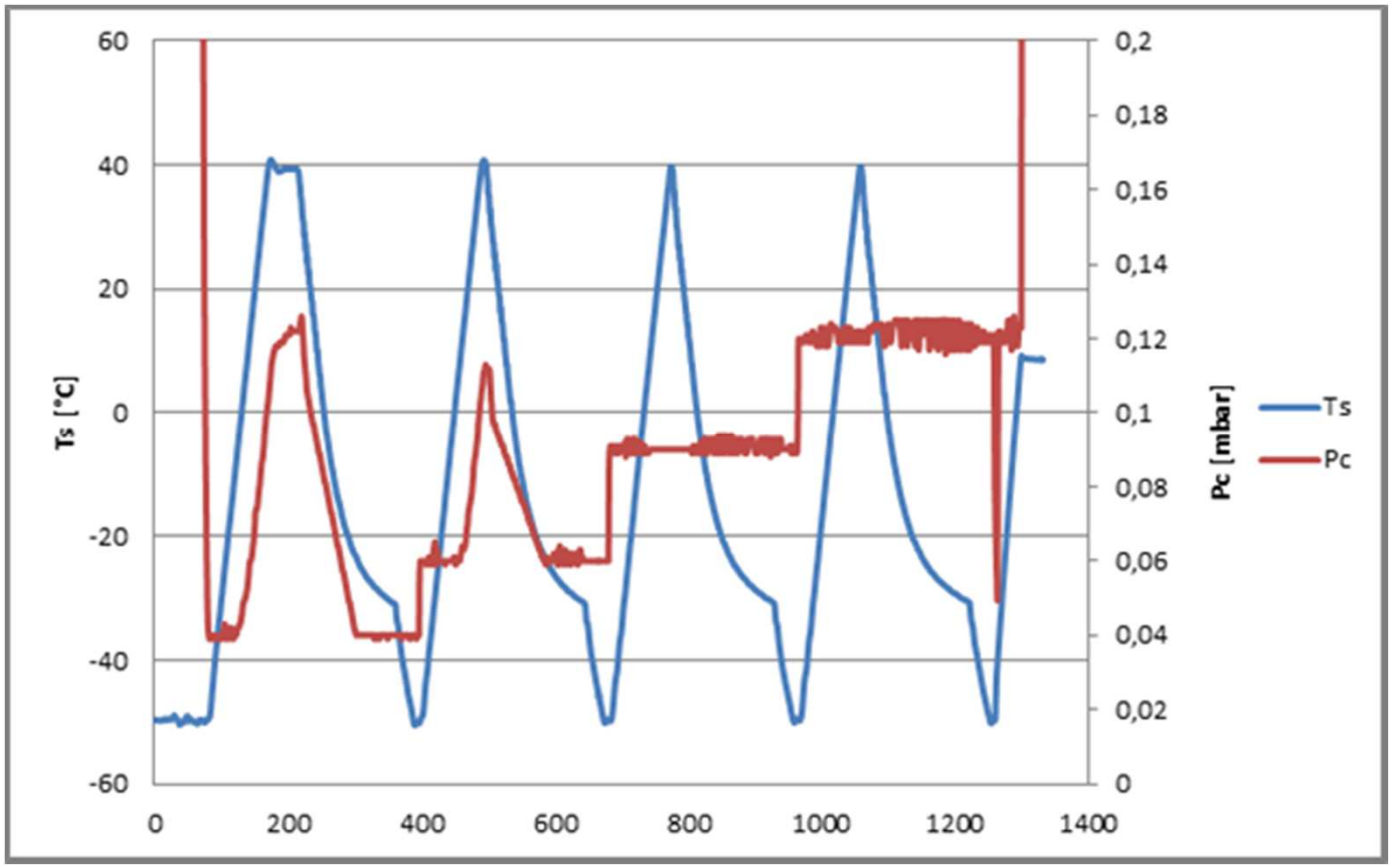


Searles J. (2010), Optimizing the Throughput of Freeze-Dryers Within a Constrained Design Space in Freeze Drying/Lyophilization of Pharmaceutical and Biological Products, 425-440

Process development

Maximum sublimation rates achievable by pilot and manufacturing freeze-dryers

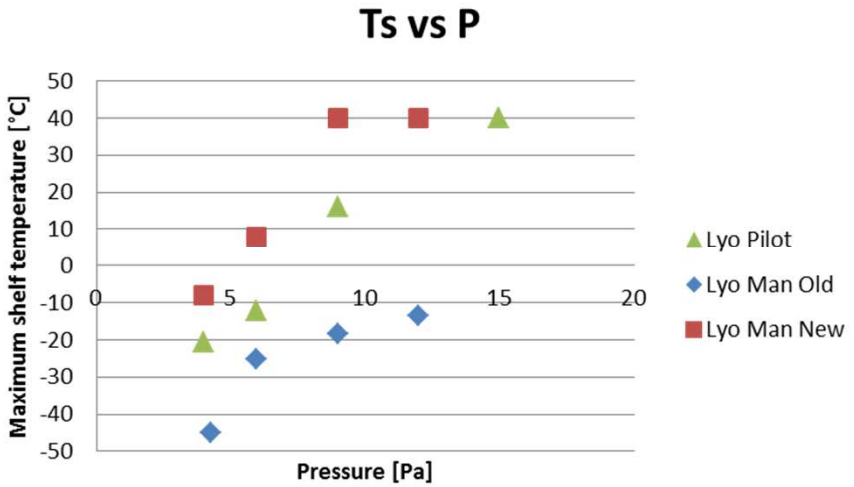
Full curve in the new commercial facility

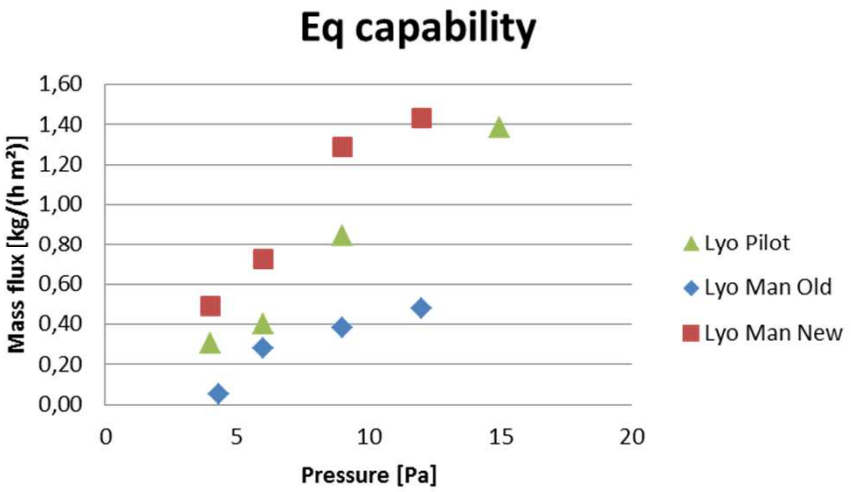


Process development

Maximum sublimation rates achievable by pilot and manufacturing freeze-dryers

Comparison between the original and the new manufacturing equipment





Differences noted between the 2 manufacturing equipments:

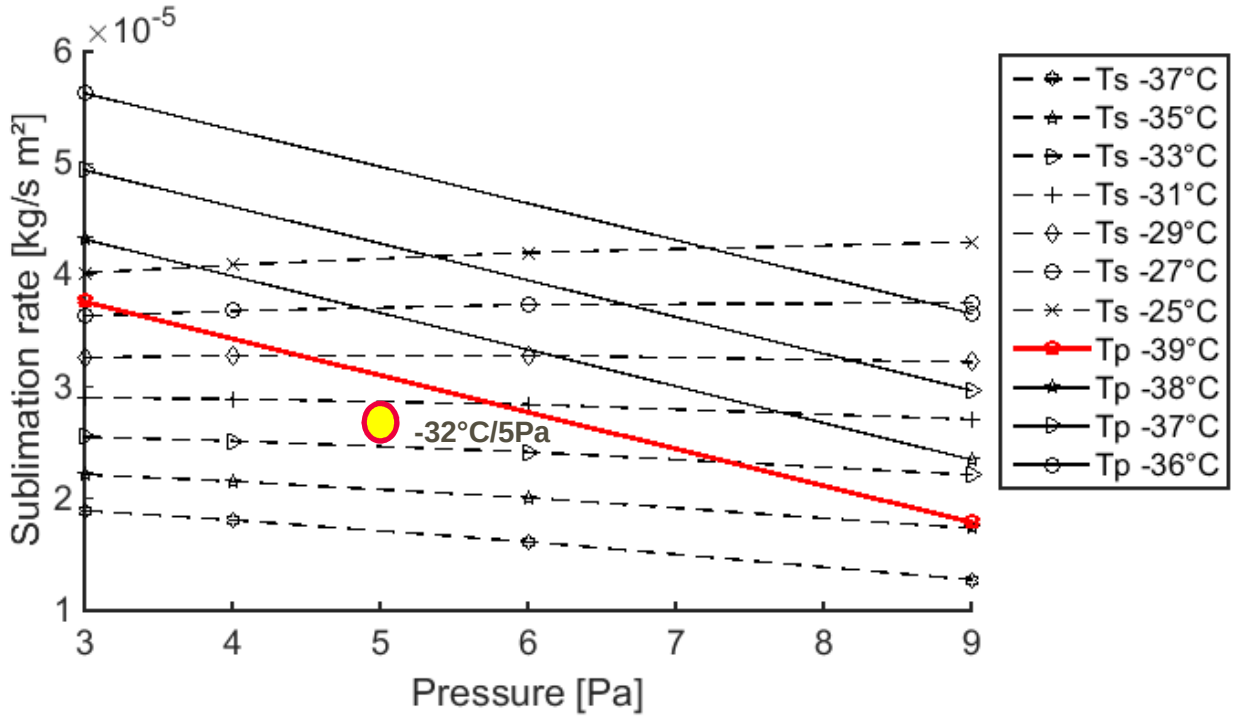
➔ Original equipment starts to lose pressure control at much lower shelf temperature than the new one

➔ Pilot scale freeze dryer loses pressure control earlier than the new commercial equipment

Process development

Design space construction

Design space was constructed at small scale according to the method described by Hardwick and Nail., 2010, Mockus et al.,2011



Knowing collapse temperature, following process parameters were selected to keep product temperature at around -40° C during the cycle (2 ° C below Tc).

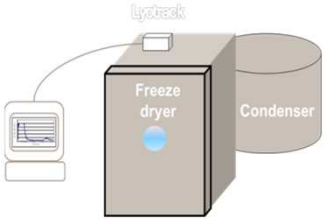
L.M. Hardwick, S.L. Nail. 2010. QbD in Process Development for Freeze-Dried Parenterals. SP-Scientific LyoLearn Webinars , www.spscientific.com\LyoTech-Center\LyoLearn-Webinars-Archive.

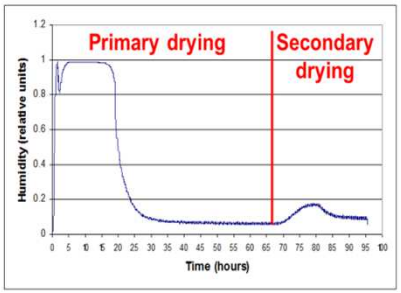
L.N. Mockus, T.W. Paul, N. Pease, N. J. Harper, P.K. Basu, E.A. Oslos, G.A. Sacha, W.Y. Kuu, L.M. Hardwick, J.Karty, M.J. Pikal, E.Hee, M.A. Khan, A.Nguyenphu, S.L. Nail. 2011. Quality by Design in Formulation and Process Development for a Freeze-Dried, Small Molecule Parenteral Product: A Case Study, Pharm Development and Technology,

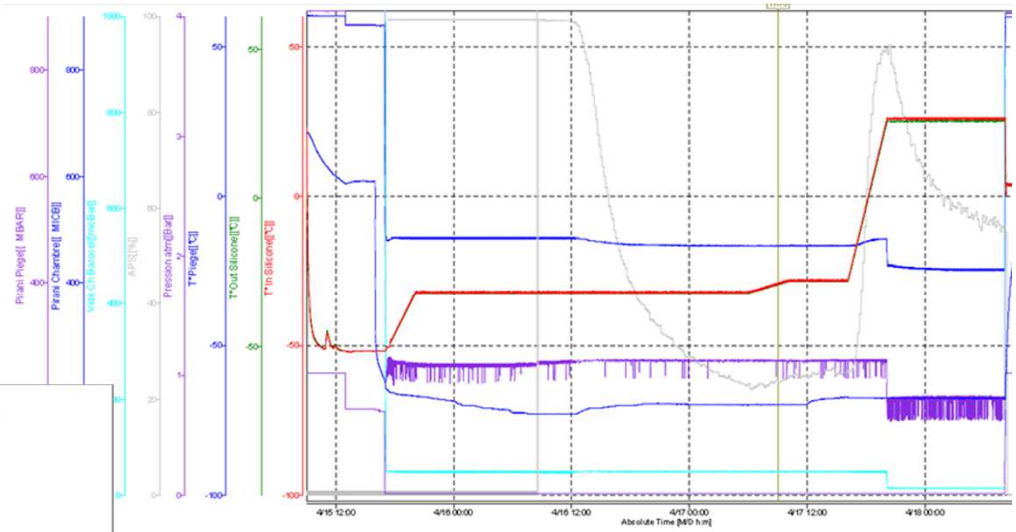
Validation of the selected process parameters at pilot scale

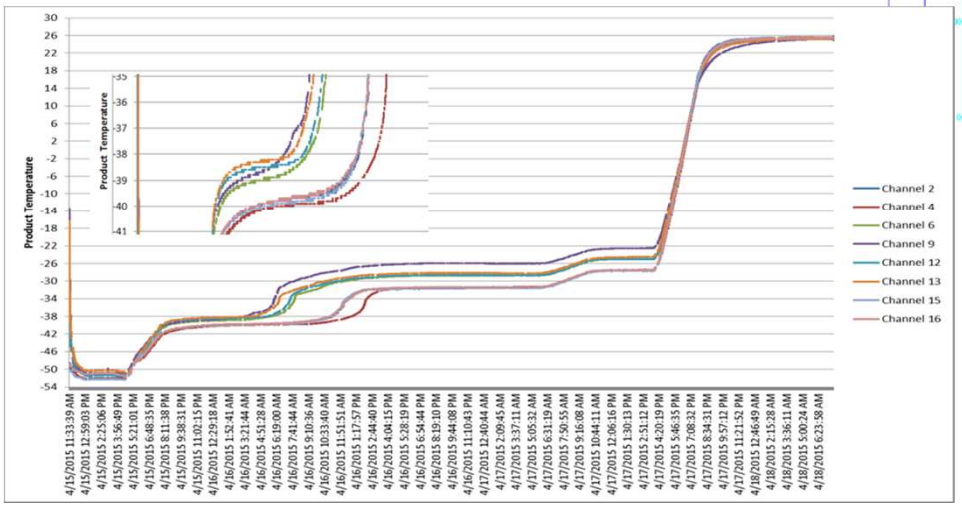
Experimental run for standard cycle

- Robustness study (n= 2500 placebo vials)
- Use of Lyotrack instrument to evaluate sublimation duration (Mayeresse, 2007), with Tempris probes placed at the edge and center of the shelves









All probes (edge and center) below collapse temperature with selected parameters. Sublimation ended before start of secondary drying

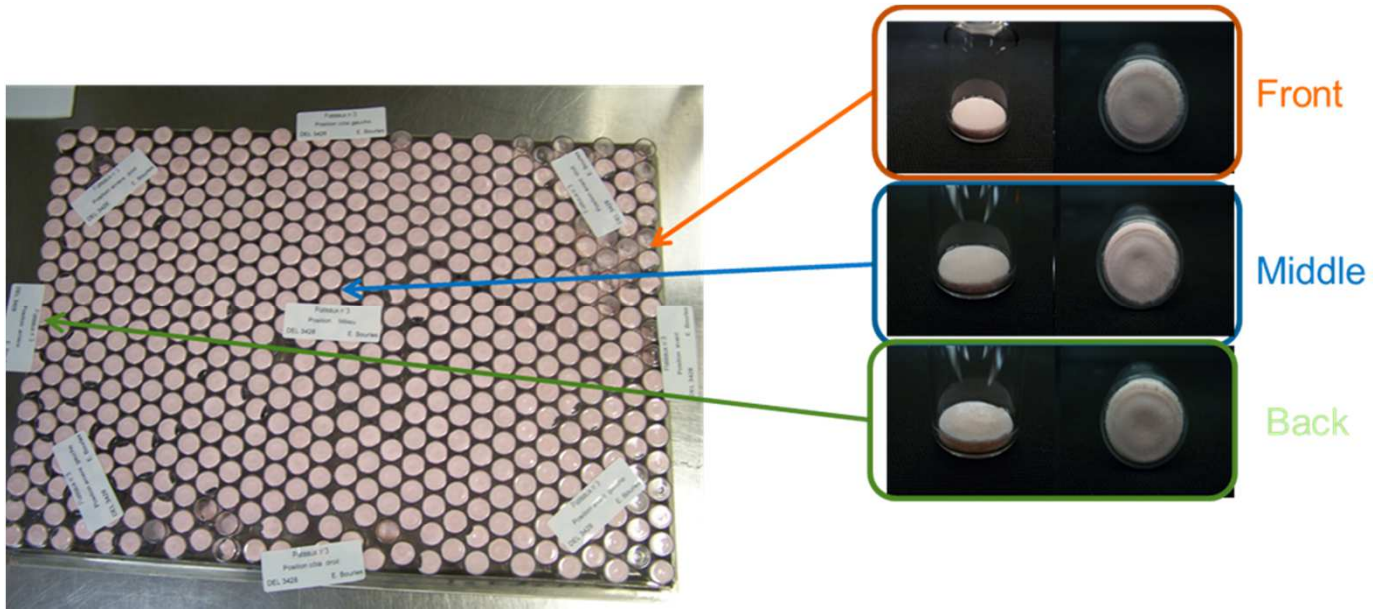
Y. Mayeresse, R. Veillon, PH. Sibille (2007) Freeze-drying Process Monitoring Using A Cold Plasma Ionization Device, PDA Journal of Pharmaceutical Science and Technology Vol. 61, No. 3, pp 160-173

Validation of the selected process parameters at pilot scale

Experimental run for standard cycle

- Robustness study (n= 2500 placebo vials)
- Use of Lyotrack instrument to evaluate sublimation duration (Mayeresse et *al*., 2007), with Tempris probes placed at the edge and center of the shelves

Shelf temperature (°C)	Pressure (Pa)	Sublimation Duration (hrs)(full saturation of the chamber)	Moisture content (%) EDGE FRONT VIALS (N=10)	Moisture content (%) CENTER VIALS (N=10)
-32	5	19	1,33 (+/-0,05)	0,95 (+/-0,05)

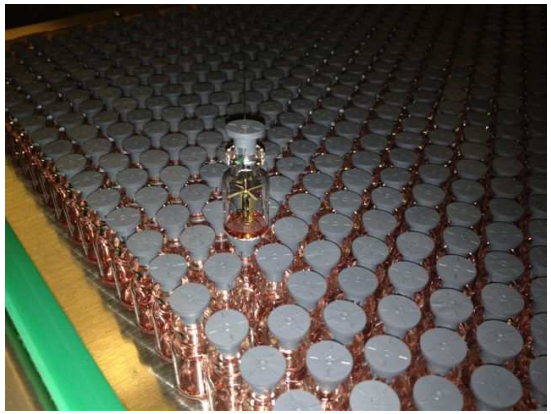


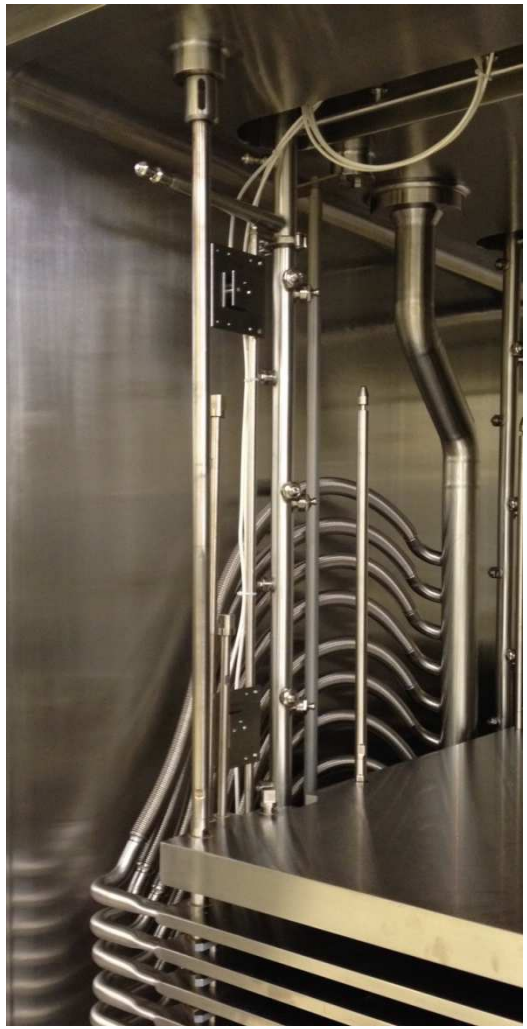
Validation of the selected process parameters at manufacturing scale

Commercial scale engineering runs

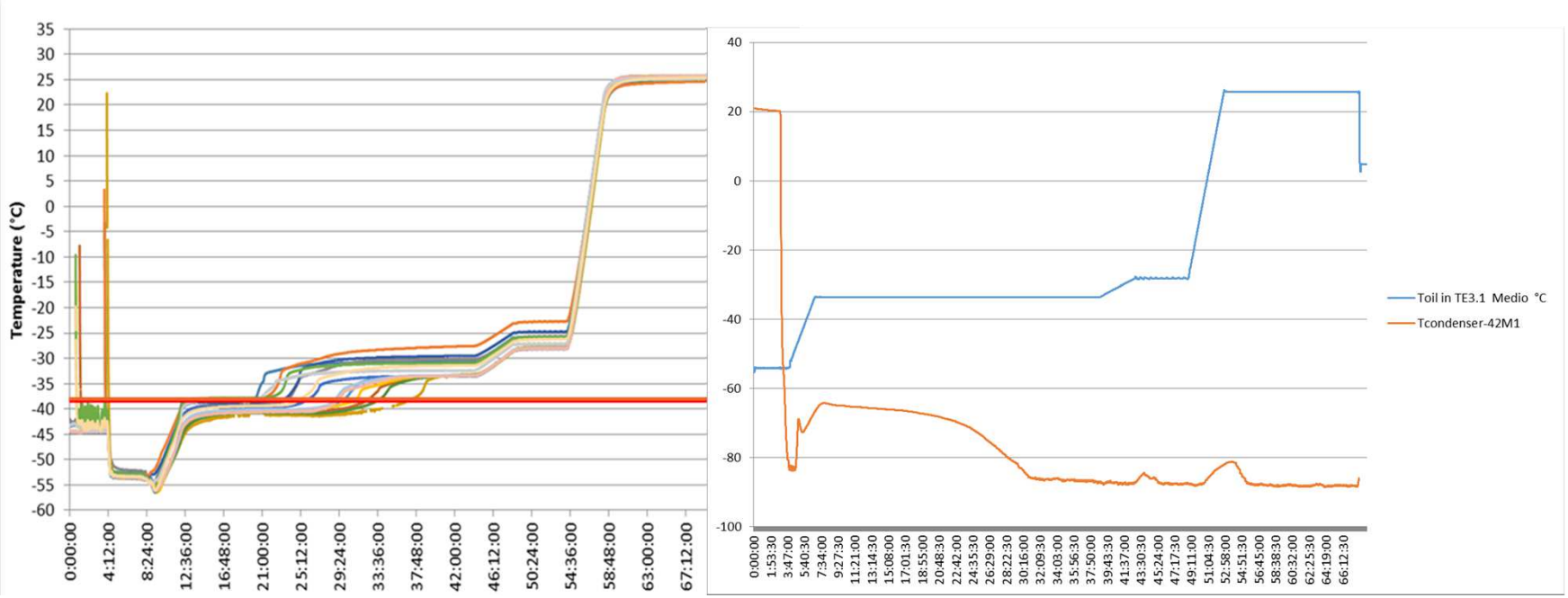
- Full load with placebo
- New freeze-drying cycle
- No capping, quick visual inspection for shortlisted shelves
- Tools: wireless probes, condenser outlet temperature
- Output:

  Product temp. Sublimation endpoint
  Thermal mapping





Validation of the selected process parameters at manufacturing scale



- Cycle used in the original manufacturing unit was modified as follow: Ts= -1,5°C/ P° -20µb

Edge effect is still visible but with minor impact ➔ rejection rate of the batch below 1%

Conclusion

- **Concrete benefit for the company:**
  - Validation batches with full rationale for freeze drying cycle
  - Rejection rate improvements ➔ Increased yield
  - Labe scale trials and surface/response modeling allow to minimize full scale technical trials ➔ Reduced cost transfer
  - Heat transfer and capability of the freeze-dryers permit a good process mapping of the equipment.

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Thank You