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Laboratory of Pharmaceutical Process Engineering

Designing a robust primary drying cycle for CVB-0217

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From vial heat transfer to a verified design space

Alpine Process Engineering Days 2026 · Montvallier · Session Lyophilisation II



Outline

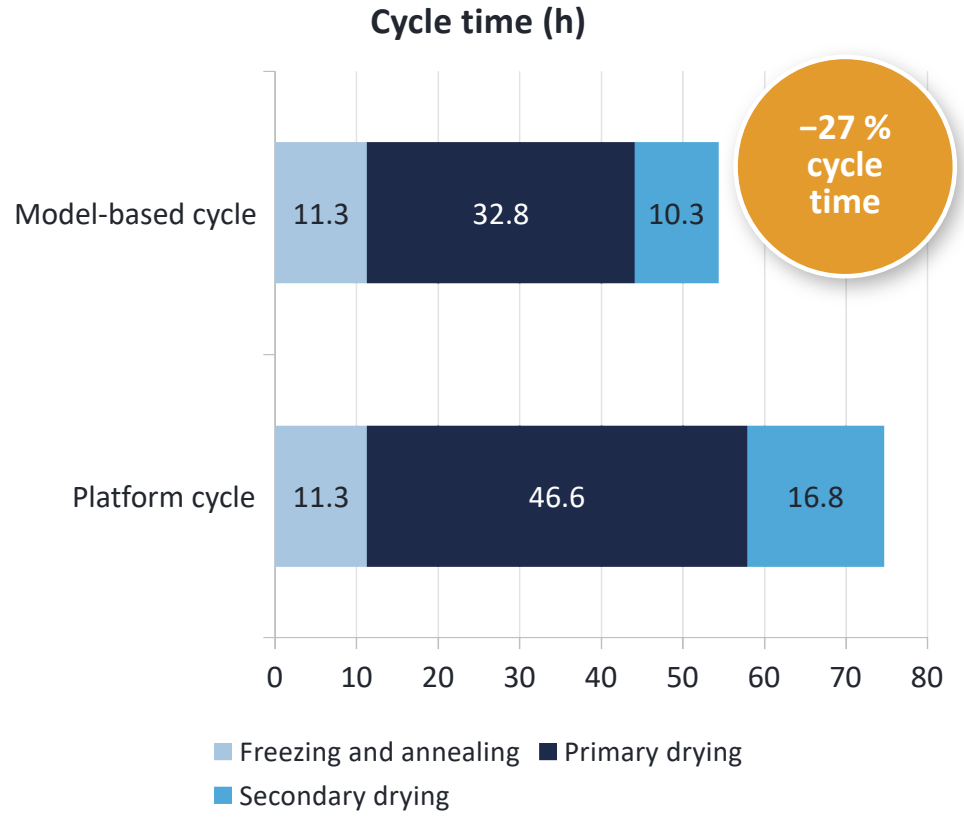
1. **Why primary drying**
   Cycle time, collapse risk and the edge-vial problem
2. **Heat transfer to the vial**
   Three mechanisms, one coefficient K_v, measured per position
3. **Mass transfer through the cake**
   Dried-layer resistance R_p from pressure-rise measurements
4. **Design space and verification**
   Model, operating ranges and three engineering runs in LY-4



10R tubing vials with 20 mm lyophilisation stoppers, as used for CVB-0217 (50 mg/mL).

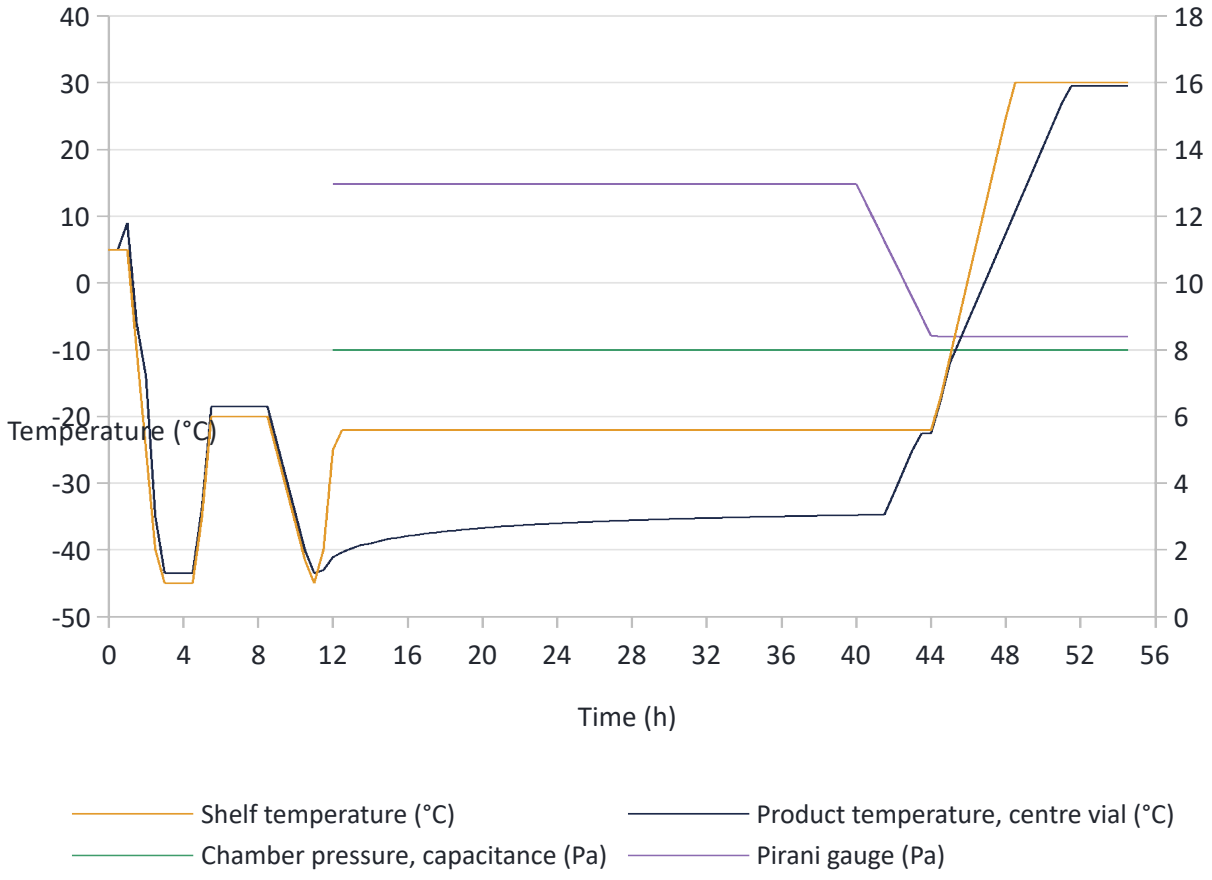
Why primary drying deserves a model

- **Longest step.** Primary drying took 62 % of the platform cycle (46.6 of 74.7 h).
- **Tight product limit.** CVB-0217 collapses at −31.5 °C (freeze-drying microscopy).
  - The platform cycle ran the product at −37.5 °C, far from the edge.
- **Position effects.** Edge vials receive extra radiation and dry up to 20 % faster, but run warmer.
- **Scale-up.** Pilot dryer results did not transfer directly to the 20 m² dryer LY-4.



Anatomy of the model-based cycle

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Freezing and annealing
0 – 11.3 h

Primary drying
11.3 – 44.1 h

Secondary drying
44.1 – 54.4 h

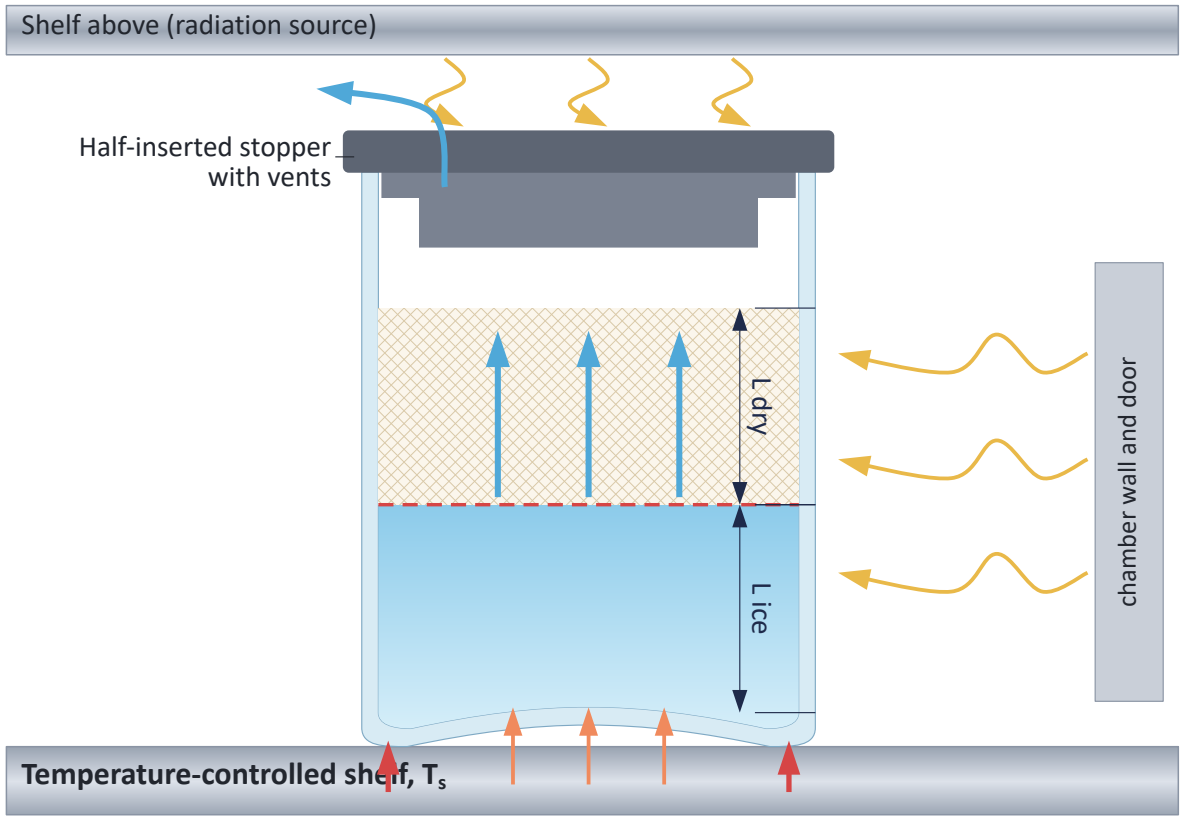
- Pirani reads high while water vapour dominates: the ratio to the capacitance gauge marks the end of primary drying.
- Product temperature peaks at −34.8 °C, 3.3 K below collapse.

01

Heat transfer to the vial

Contact conduction, gas conduction and radiation, lumped into one vial heat-transfer coefficient K_v that depends on chamber pressure and on the position of the vial on the shelf.

Three paths for heat, one for vapour



Qc contact conduction
through the contact ring of the vial bottom

Qg gas conduction
across the gap under the concave bottom; rises with Pc

Qr radiation
from the upper shelf, walls and door; strongest at the edge

Vapour flow
from the sublimation front through the dried cake and the stopper vents

Sublimation front
at temperature T_p, moving down as the ice disappears

Vial heat-transfer coefficient

HEAT FLOW TO ONE VIAL

$$\dot{Q} = A_v K_v (T_s - T_b)$$

PRESSURE-DEPENDENT HEAT-TRANSFER COEFFICIENT

$$K_v = K_C + K_R + \frac{K_D P_c}{1 + l P_c}$$

ENERGY BALANCE AT THE SUBLIMATION FRONT

$$\dot{Q} = \Delta H_s \dot{m}$$

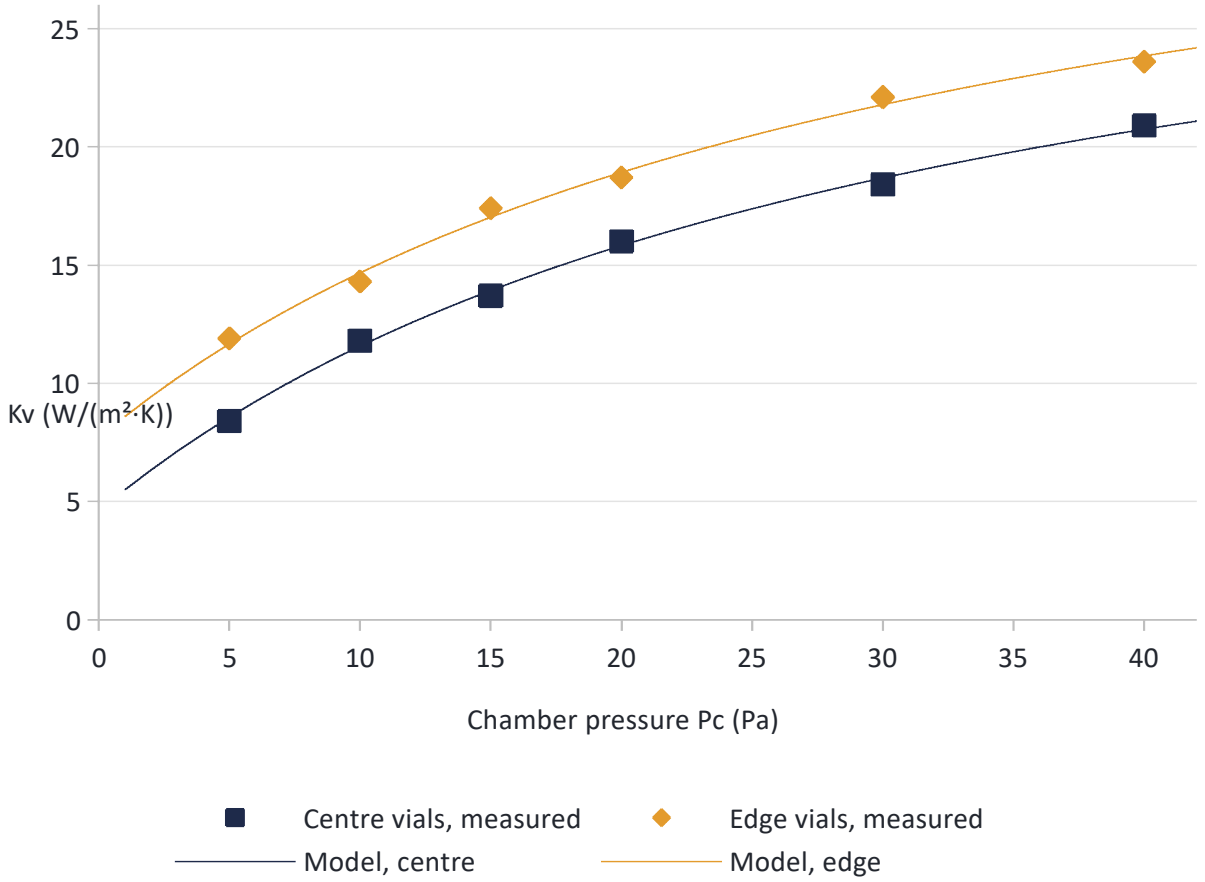
TEMPERATURE DROP ACROSS THE FROZEN LAYER

$$T_b - T_p = \frac{\dot{Q} L_{ice}}{A_p \lambda_{ice}}$$

Parameter	Centre	Edge	Unit
$K_C + K_r$	4.6	7.7	W/(m²·K)
KD	0.92	0.92	W/(m²·K·Pa)
l	0.032	0.032	1/Pa
A_v (outer bottom)	4.71	4.71	cm²
A_p (inner section)	3.80	3.80	cm²
ΔH_s	2 840	2 840	J/g

K_v measured gravimetrically in 6 runs at 5–40 Pa with pure ice in 360 vials per run; the edge offset of +3.1 W/(m²·K) is the extra radiation from the door and the walls of LY-4.

K_v rises with pressure, and with exposure



- **Gas conduction** explains the rise with pressure; it saturates above 30 Pa as the mean free path of water vapour becomes small compared to the gap.
- **Edge vials** show a constant offset of +3.1 W/(m²·K): radiation, not conduction.
- **Residual scatter** of ±0.6 W/(m²·K) (1 σ) reflects vial bottom curvature; we use the upper 95 % bound for the design space.

02

Mass transfer through the dried layer

The dried cake resists the vapour flow more as it grows: R_p is the second key parameter, measured by pressure rise in the dryer.

Sublimation rate and dried-layer resistance

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SUBLIMATION RATE THROUGH THE DRIED CAKE

$$\dot{m} = \frac{A_p (P_{ice} - P_c)}{R_p}$$

DRIED-LAYER RESISTANCE GROWS WITH THE CAKE

$$R_p = R_0 + \frac{A_1 L_{dry}}{1 + A_2 L_{dry}}$$

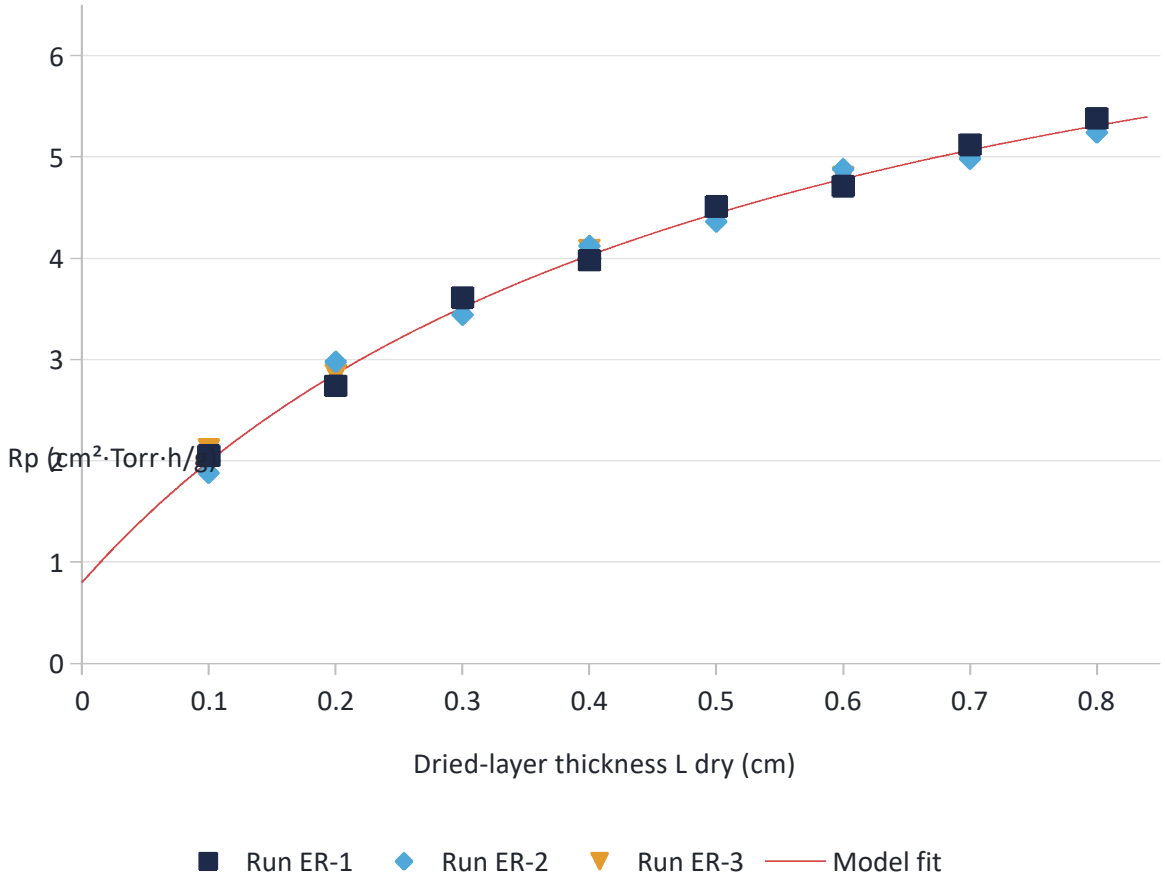
VAPOUR PRESSURE OF ICE AT THE FRONT

$$\ln \frac{P_{ice}}{Pa} = 28.9074 - \frac{6144.96}{T_p / K}$$

Parameter	Value	Unit
R_0	0.80	cm²·Torr·h/g
A_1	14.2	cm·Torr·h/g
A_2	1.9	1/cm
L total (3.2 mL fill)	0.84	cm
Solid content	10.3	% w/v

Combining the heat and mass balances gives one equation in T_p for every shelf temperature, chamber pressure and dried-layer thickness. We solve it by bisection; the worst case is the end of primary drying, when R_p is highest and the ice layer is thin.

R_p from pressure-rise measurements



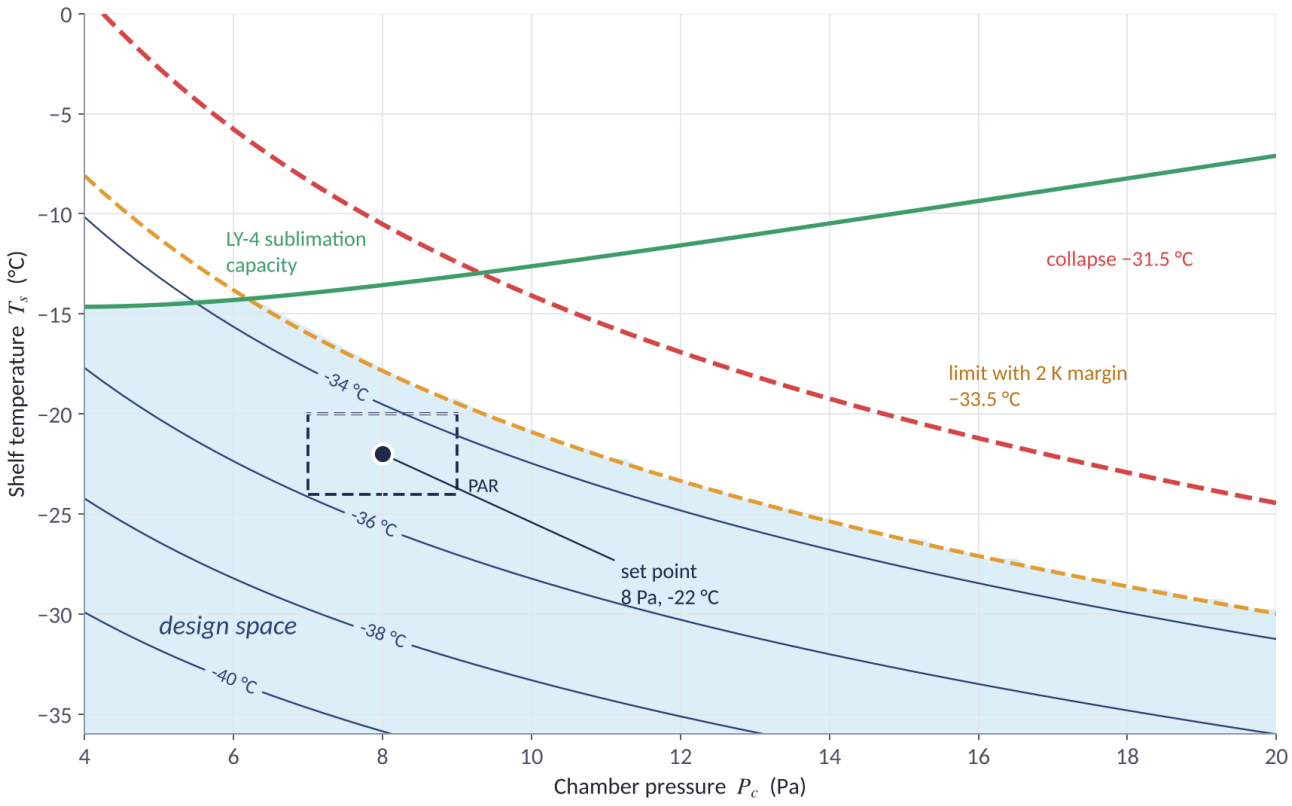
- **Pressure rise** every 2 h: valve to the condenser closed for 25 s, pressure rise fitted to obtain Pice and R_p.
- **Three runs agree** within ±4 %: the cake structure is reproducible after annealing at −20 °C.
- **Without annealing** R_p was 35 % higher and scattered twice as much (not shown).

03

Design space and verification

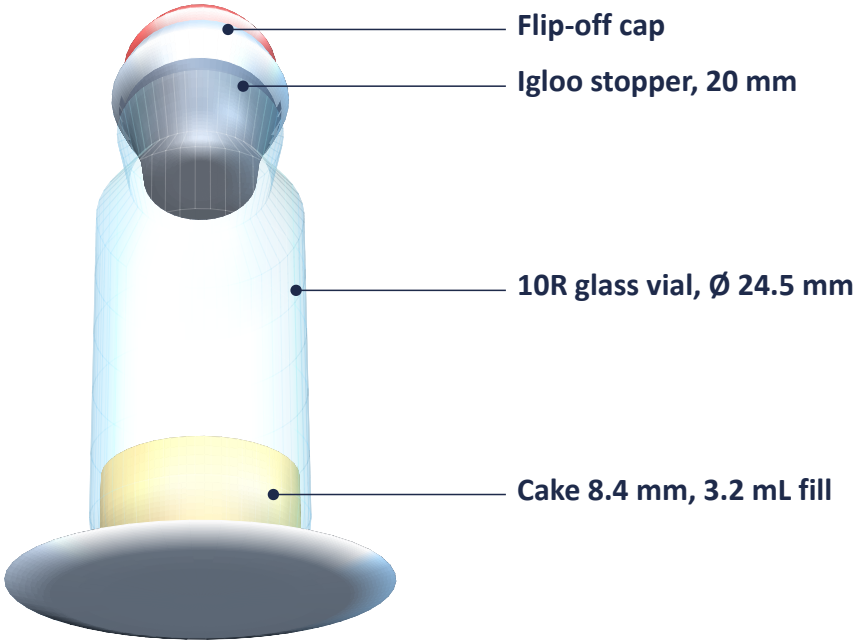
Mapping the product temperature over shelf temperature and chamber pressure, adding the equipment limit, and checking the result in the commercial dryer.

Primary drying design space for LY-4

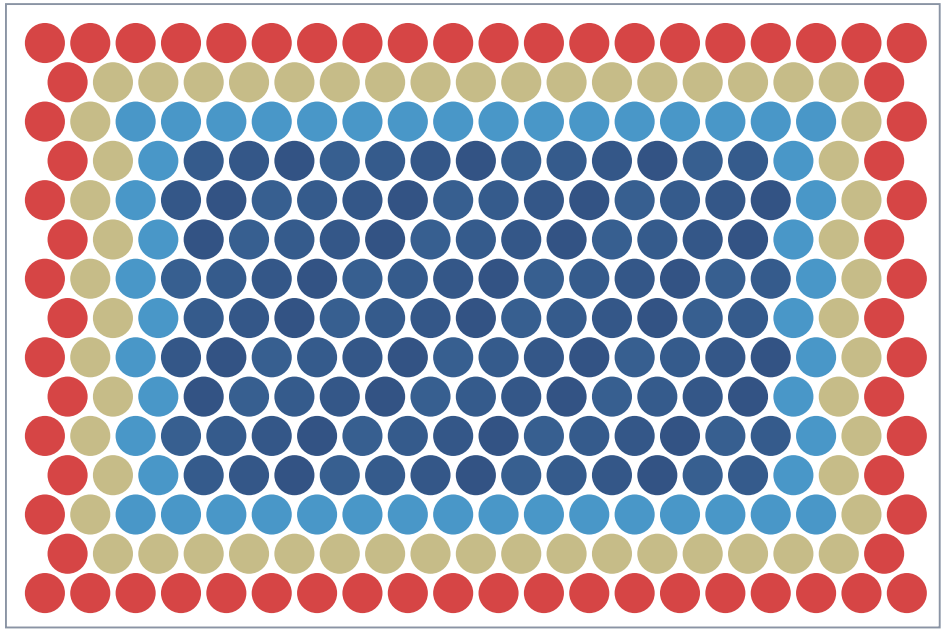


- **Product limit:** T_p at the end of primary drying ≤ −33.5 °C (collapse −31.5 °C, 2 K margin).
- **Equipment limit:** LY-4 condenser and duct capacity, measured in ice-slab runs.
- **Set point** -22 °C / 8 Pa; proven acceptable range ±2 K and ±1 Pa.
- **Worst corner** of the PAR (−20 °C, 9 Pa): T_p = -33.7 °C, inside the limit.

One vial, 36 500 vials



One LY-4 shelf (detail): predicted end of primary drying





The model-based cycle, step by step

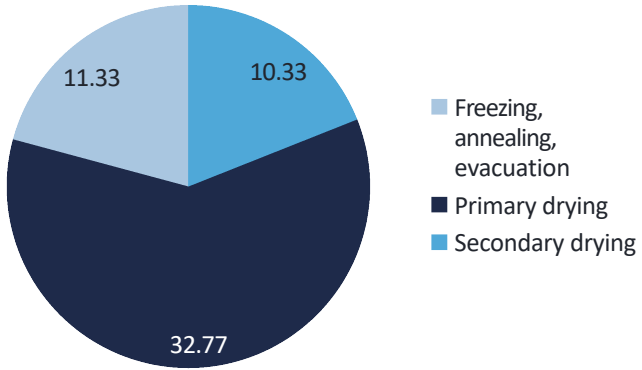
#	Step	Shelf (°C)	Rate (K/min)	Pc (Pa)	Time (h)
1	Loading	+5	–	atm	1.00
2	Freezing ramp	+5 → −45	0.5	atm	1.67
3	Freezing hold	−45	–	atm	2.00
4	Annealing ramp	−45 → −20	0.5	atm	0.83
5	Annealing hold	−20	–	atm	3.00
6	Re-freezing, ramp and hold	−20 → −45	0.5	atm	2.33
7	Evacuation	−45	–	8	0.50
8	Primary drying ramp	−45 → −22	0.5	8	0.77
9	Primary drying hold	−22	–	8	32.00
10	Secondary drying ramp	−22 → +30	0.2	8	4.33
11	Secondary drying hold	+30	–	8	6.00
	Total cycle				**54.43**

Primary drying (rows 8–9)

Model end point: centre vials 29.7 h, edge vials 24.7 h after the start of the hold.

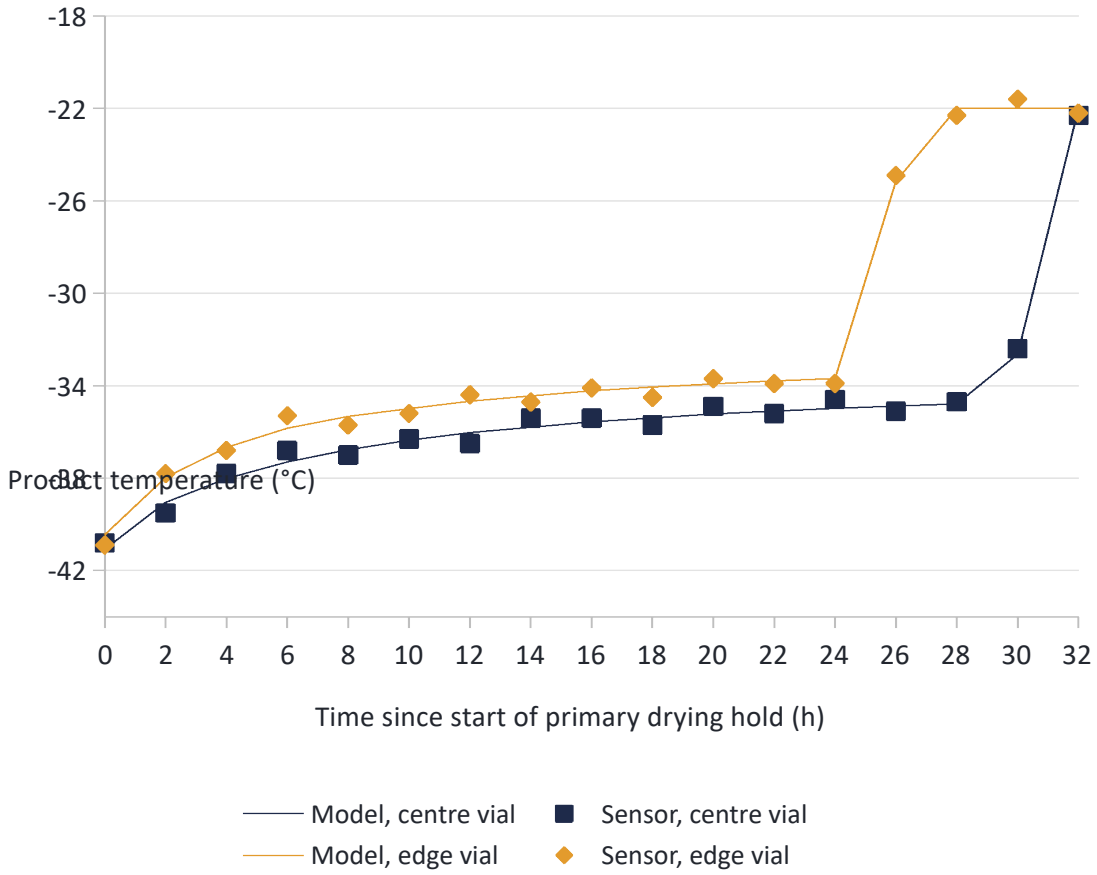
Hold set to 32 h (+8 %), end confirmed by the Pirani / capacitance ratio < 1.05.

Annealing at −20 °C for 3 h grows larger ice crystals and lowers R_p by about a third.



Verification in LY-4: model against sensors

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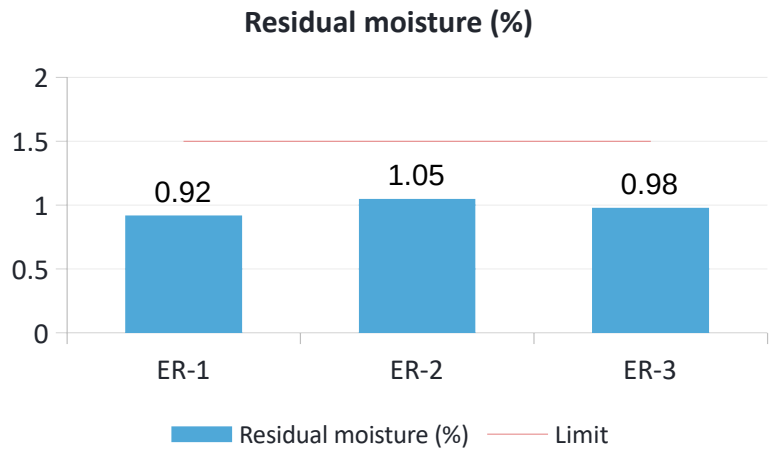


LY-4, 20 m² shelf area, Corvane Visp site

- **Maximum deviation** model to sensor 0.9 K (centre), 1.2 K (edge).
- **End of primary drying** within 1.5 h of prediction in all three runs.

Three runs, three conforming batches

	ER-1	ER-2	ER-3	Specification
Vials loaded	35 900	36 500	36 480	–
Max. T_p, edge vials (°C)	−33.8	−33.5	−33.9	< −31.5
End of primary drying (h)	30.4	29.9	31.1	≤ 32
Residual moisture (%)	0.92	1.05	0.98	≤ 1.5
Reconstitution time (s)	48	52	45	≤ 120
Cake appearance	elegant	elegant	elegant	no collapse
Monomer by SEC (%)	99.1	99.2	99.0	≥ 98.0



Outcome

All quality attributes met with margin; ER-2 and ER-3 released for clinical supply.

Cycle registered in the CVB-0217 dossier with the design space as a proven acceptable range.

Take-home messages

1

Measure K_v per position.

Edge and centre differ by a constant radiation term; use the centre for the end point and the edge for the temperature limit.

2

Anneal to control R_p.

Three hours at −20 °C made the cake resistance reproducible within ±4 %.

3

Design for the worst moment.

The end of primary drying, with the highest R_p, sets the product temperature limit.

4

Verify at scale.

Three LY-4 runs matched the model within 1.2 K and 1.5 h, with a 27 % shorter cycle.

References

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Thank you. Questions?

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