SMART Freeze Drying of Highly Concentrated Amorphous Systems: Comparison of MTM-Based vs. TDLAS-Based Methods

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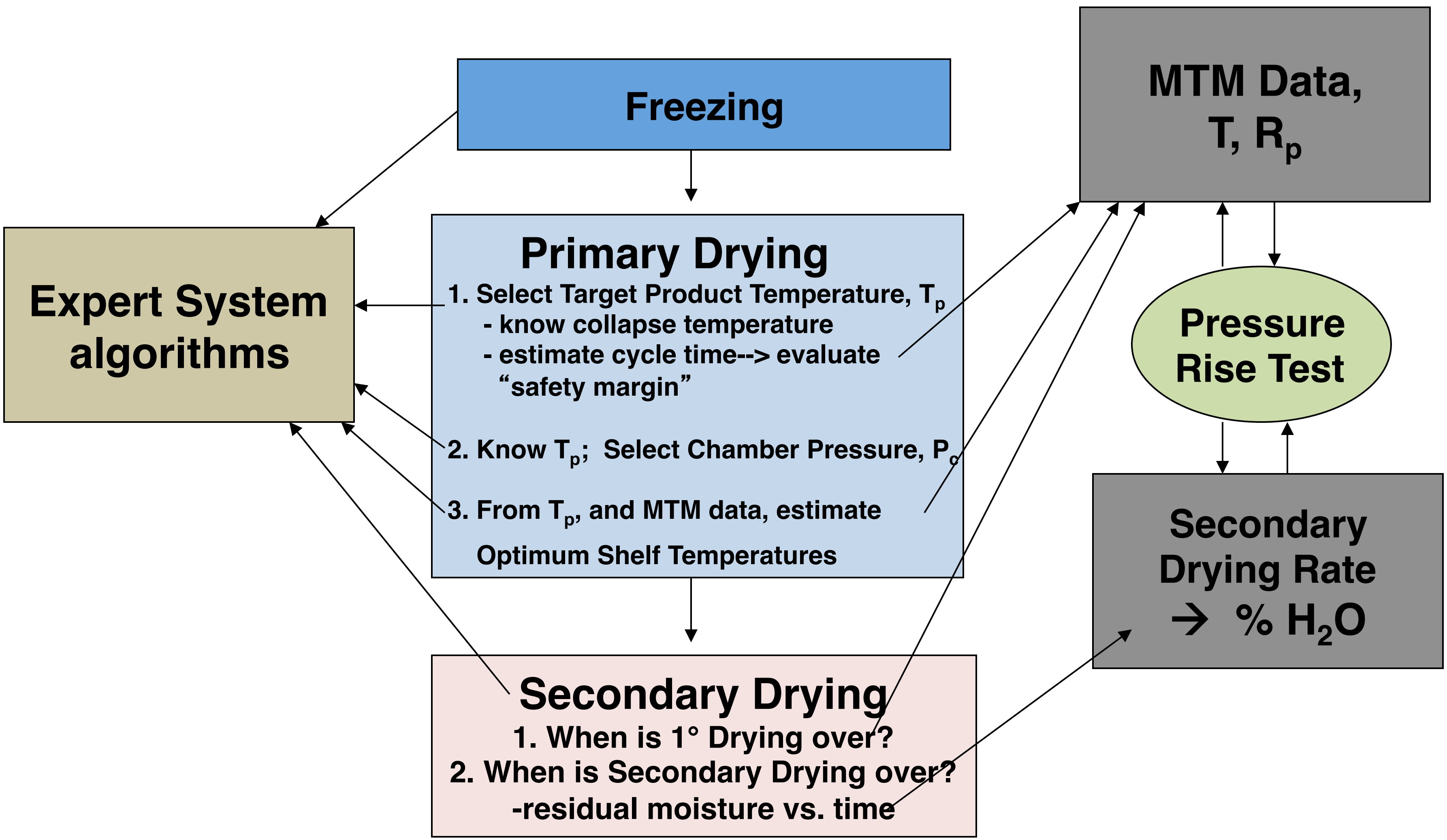
TDLAS-Based "Smart Freeze Dryer"

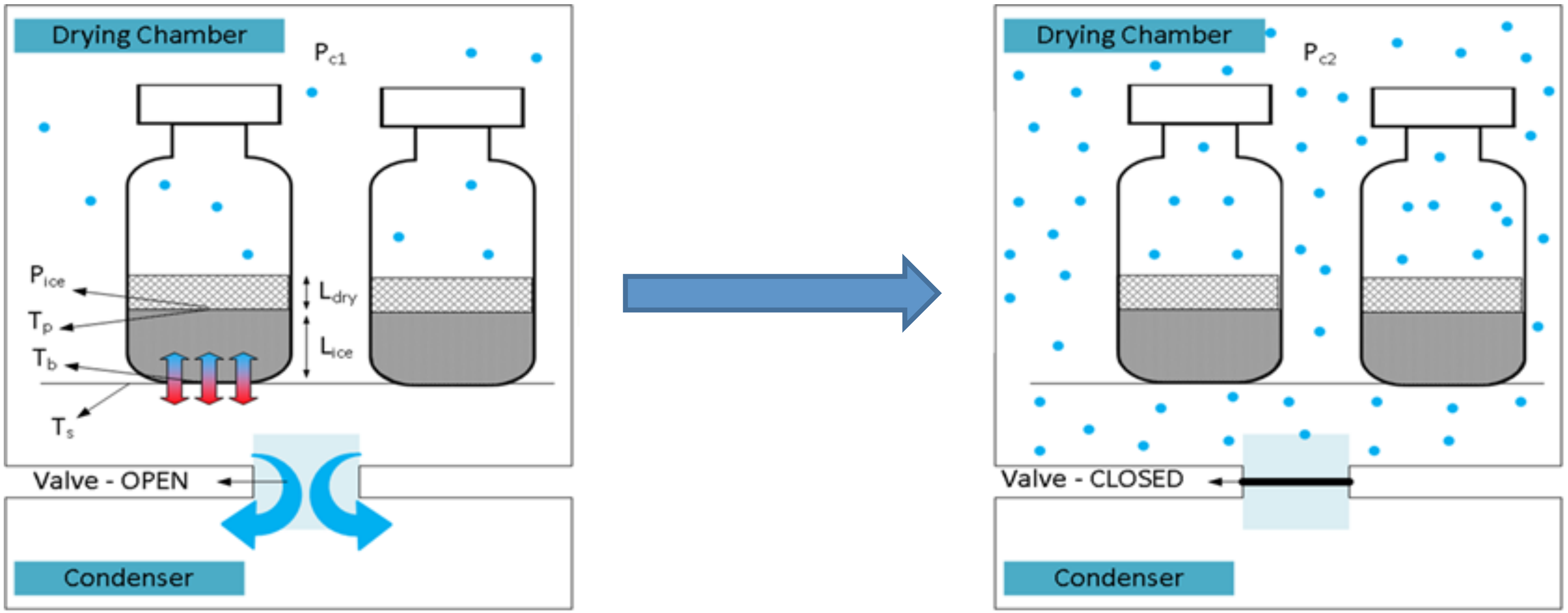
- Smart Freeze Dryer Concept
  - Develop "optimum" process in one laboratory experiment
    - Data from process plus Expert System algorithms
  - Current Smart Freeze Dryer operates on MTM
    - Evaluate mass flow and product T
  - Works well in most cases,
    - but not with high concentration of amorphous solid
  - TDLAS method uses mass flow monitor for mass flow and product T
    - Should give good results in all cases

Operation of the Smart Freeze Dryer



Manometric Temperature Measurement (MTM)

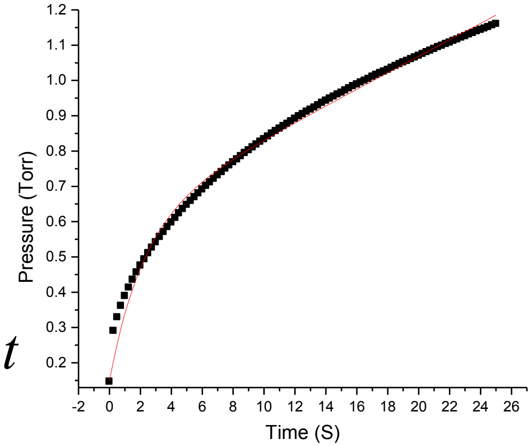
- MTM analysis involves quickly isolating the freeze chamber from the condenser (~25 sec) and analyzing the resultant pressure rise in drying chamber



Manometric Temperature Measurement (MTM)

- **MTM analysis involves quickly isolating the freeze chamber from the condenser (~25 sec) and analyzing the resultant pressure rise in drying chamber**

$$P(t) = P_{ice} - (P_{ice} - P_0)\cdot \exp\left[-\left(\frac{3.461\cdot N\cdot A\cdot T_v}{V\cdot(\hat{R}_p + \hat{R}_s)}\right)\cdot t\right] + 0.465\cdot P_{ice}\cdot \Delta T\cdot\left[1 - 0.811\cdot\exp\left(-\frac{0.114}{L_{ice}}\cdot t\right)\right] + Ex\cdot t$$



- **Pressure at the sublimation interface (P_{ice})**
- **Mass transfer resistance (R_p)**
- **Temperature at the sublimation interface (T_{sub})**
- **Temperature at vial bottom (T_b)**
- **Vial heat transfer coefficient (K_v)**
- **Heat transfer into the product (dQ/dt)**
- **Sublimation rate (dm/dt)**

MTM is meant to evaluate "representative" product temperature during freeze drying, without placing thermocouples into product vials

Tang X. C. *et al*, Pharm. Res.; 22: 685-700 (2005)
Gieseler, H. *et al*, J. Pharm. Sci., 96: 3402-3418 (2007)

Manometric Temperature Measurement (MTM)

Advantages

- MTM technique gives product temperature of the batch as a whole and does not require insertion of temperature sensors into the vials
  - Works well for many typical formulations
    - Crystalline solutes
    - 5% sucrose, …
- Assessment of critical process attributes
  - Mass transfer resistance (Rp)
  - Vial heat transfer coefficient (Kv)
  - Sublimation rate (dm/dt)

Disadvantages

- Requires the periodic disruption of the drying process
- Not easily installed in manufacturing
- MTM may fail in cases of high levels of amorphous solids after creation of a significant dry layer
  - due to water re-absorption, MTM temperature is too low after a few hours of primary drying

Temperature and Resistance Comparison Between MTM and Thermocouples

For Crystalline and *high concentration* Amorphous

Materials	T_s	P_0	T_{MTM}	T_{TC}	R_{MTM}	$R_{gravimetric}$
			Temp Compare		Resistance Compare	
Glycine	-20	80	-33.6	-32.7	3.1	3.4
Glycine	+37	120	-23.6	-24	2.7	2.6
Mannitol	+40	300	-8.8	-9.1	8.0	8.4
Amorphous I	+31	143	-22.2	-17	8.3	8.4
Amorphous II	+16	85	-33.0	-26	2.8	3.3

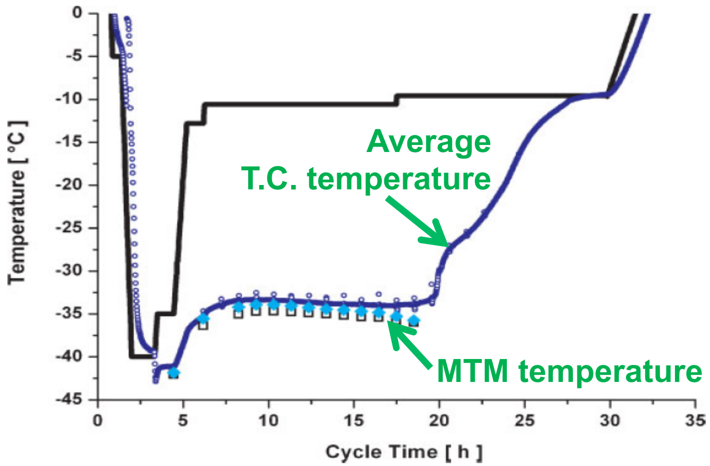
- **Good agreement for crystalline solids, poor for high concentration amorphous- due to water re-sorption!**

Data from: "Evaluation of Manometric Temperature Measurement (MTM), a Process Analytical Technology Tool in Freeze Drying: The Impact of Water Re-Absorption", Tang, Pikal, and Nail, manuscript in preparation

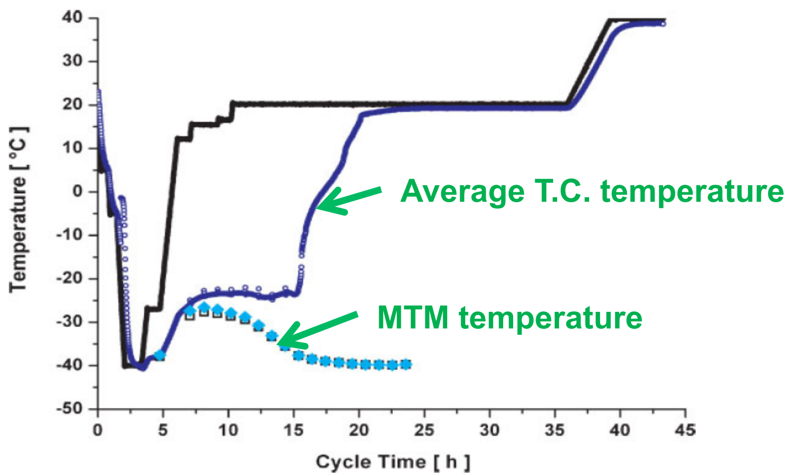
Manometric Temperature Measurement (MTM)

- ❖ For amorphous solutes - MTM under-predicts the product temperature, especially at high amorphous concentration

Sucrose 5% – Small MTM error



PVP 5% – Large MTM error



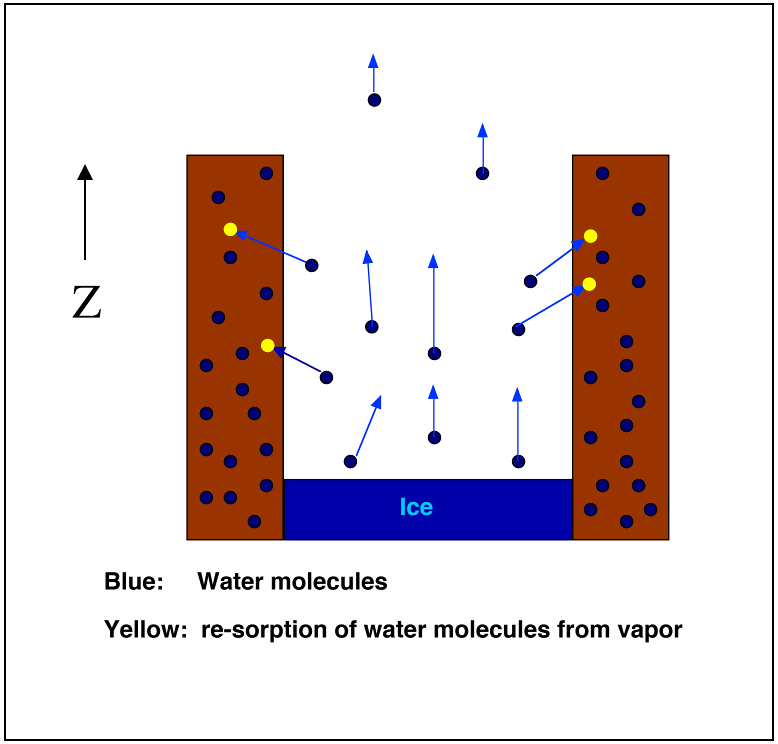
- ❖ **Due to water resorption by amorphous solutes partially dried layer**

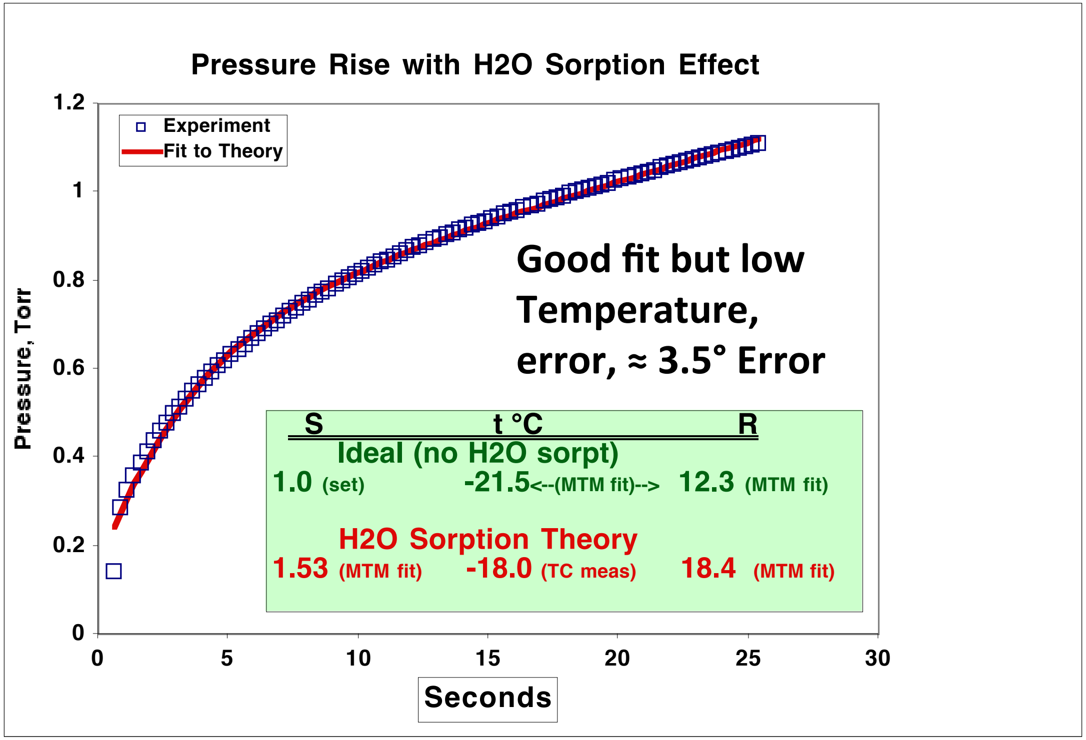
Gieseler, H. *et al*, J. Pharm. Sci., 96: 3402-3418 (2007)

Re-Sorption of H_2O:

Not all water sublimed reaches the chamber

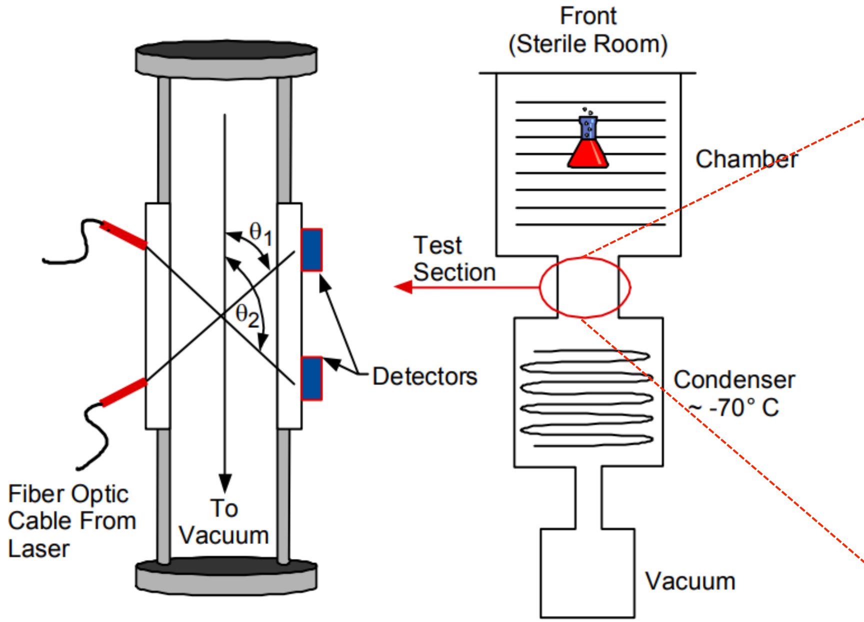
High Concentration Amorphous solid

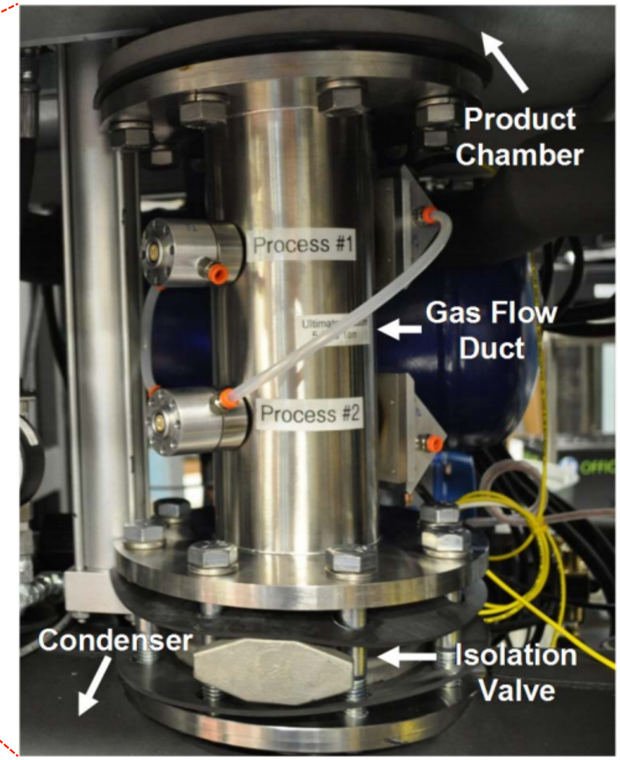




Tunable Diode Laser absorption spectroscopy (TDLAS)

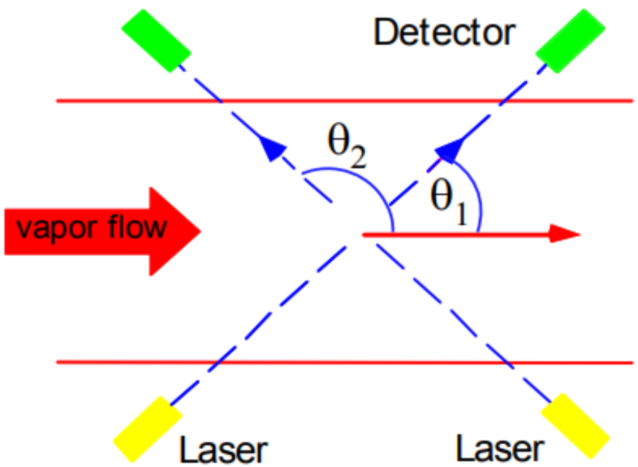
- Tunable Diode Laser Absorption Spectroscopy (TDLAS) is an optical method for detecting trace concentrations of one or more selected gases mixed with other gases.



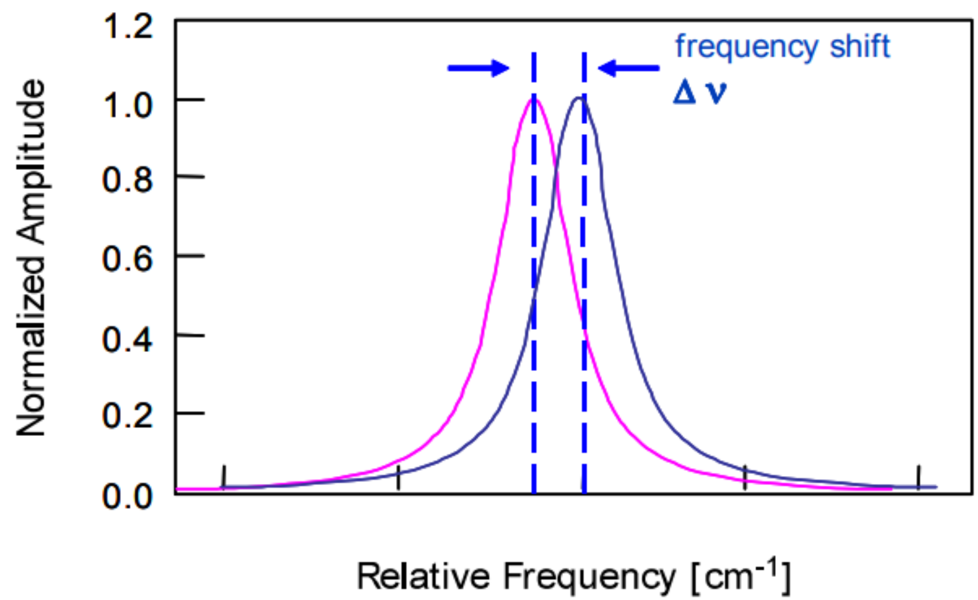


- **Advantages:**
  - **Does not require any probes to be inserted in the dryer equipment**
  - **Can be implemented on laboratory, pilot and production scale freeze-dryers**
  - **Continuous, real-time, nonintrusive**

Gas Mass Flow and Velocity



Doppler shifted absorption lineshape measurement



density

$$\rho = \frac{\int_{0}^{\nu} \ln(I/I_o)\, d\nu}{S\ell} \quad [g/cm^3]$$

Determined using absoption line-strength, pathlength, integrated Area and the laser frequency increment

velocity

$$u = \frac{\Delta\nu\, c}{\nu_o\,(\cos\theta_1 - \cos\theta_2)} \quad [cm/s]$$

Determined using Doppler shift, speed of light, measurement angle and transition frequency

mass flow

$$dm/dt = u \cdot \rho \cdot A \quad [g/s]$$

Determined using velocity, density and duct cross-sectional area

TDLAS Measure of Product Temperature

❖ Steady State Heat and Mass Transfer Model

$$\begin{cases} dQ/dt = A_V \cdot K_V \cdot (T_S - T_b) \\ dQ/dt = \Delta H_S \cdot dm/dt \end{cases}$$

dQ/dt	: heat flow (cal/s)
dm/dt	: sublimation rate
ΔH_s	: water heat of sublimation
A_v	: cross sectional area of vials
K_v	: vial heat transfer coefficient
T_s	: shelf temperature
T_b	: product temperature at vial bottom

❖ Product Temperature Determinations

$$\begin{cases} T_b = T_S - \left[\dfrac{(\Delta H_S \cdot (dm/dt))}{A_V \cdot K_V} \right] \\ K_v = \Delta H_s (dm/dt)/(A_v \ (T_s - T_p)) \end{cases}$$

- ➢ Through the combination of TDLAS measurements and a well-established heat and mass transfer model describing freeze drying, Tb or Kv can be acquired interchangeably.
- ➢ Input Kv accounts for all sources of heat & is weighted average of edge and center vials.
- ➢ Accurate, non-intrusive determination of batch average product temperature.

TDLAS Measured Temperature is not quite the "Average Temperature"

- TDLAS determines temperature by input of sublimation rate (via TDLAS) and vial heat transfer coefficient, but,
  - Edge vials contribute more to the sublimation rate than their numbers would suggest, since they sublime faster

$$T_p^{TDLAS} = r \cdot T_p^E + (1-r) \cdot T_p^c,$$

$$r = \frac{f_E \cdot K_v^E}{\left(f_c \cdot K_v^c + f_E \cdot K_v^E\right)}$$

The Difference between Number Average Product Temperature and TDLAS average is small

Formulation	Mean Tb (TC)	Tb TDLAS	TDLAS Bias
Sucrose-Protein	-26.75	-26.65	0.11
Sucrose	-31.25	-31.08	0.17
Mannitol	-13.91	-13.83	0.08

- **Fortunately, the difference (bias) is expected to normally be quite small, less than the actual experimental error due to errors in sublimation rate and Kv**

Experimental Error in TDLAS T_b

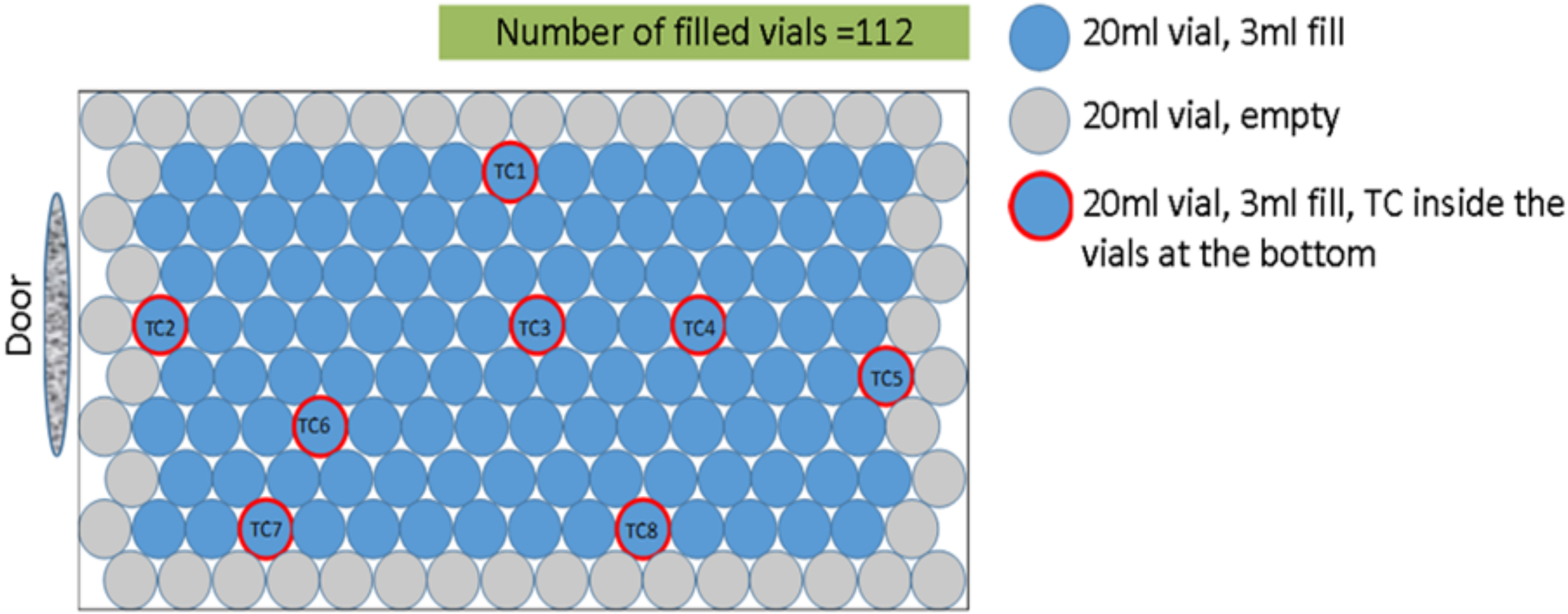
$$\sigma T_p = (T_s - T_p)\sqrt{\cdot\left(\frac{\sigma K_v}{K_v}\right)^2 + \left(\frac{\sigma \dot{Q}}{\dot{Q}}\right)^2}$$

Estimate ≈ 3% Error in both Kv and Q

Formulation	Error TDLAS T_b
Sucrose protein (1:1)	0.71
Sucrose	0.39
Mannitol	1.01

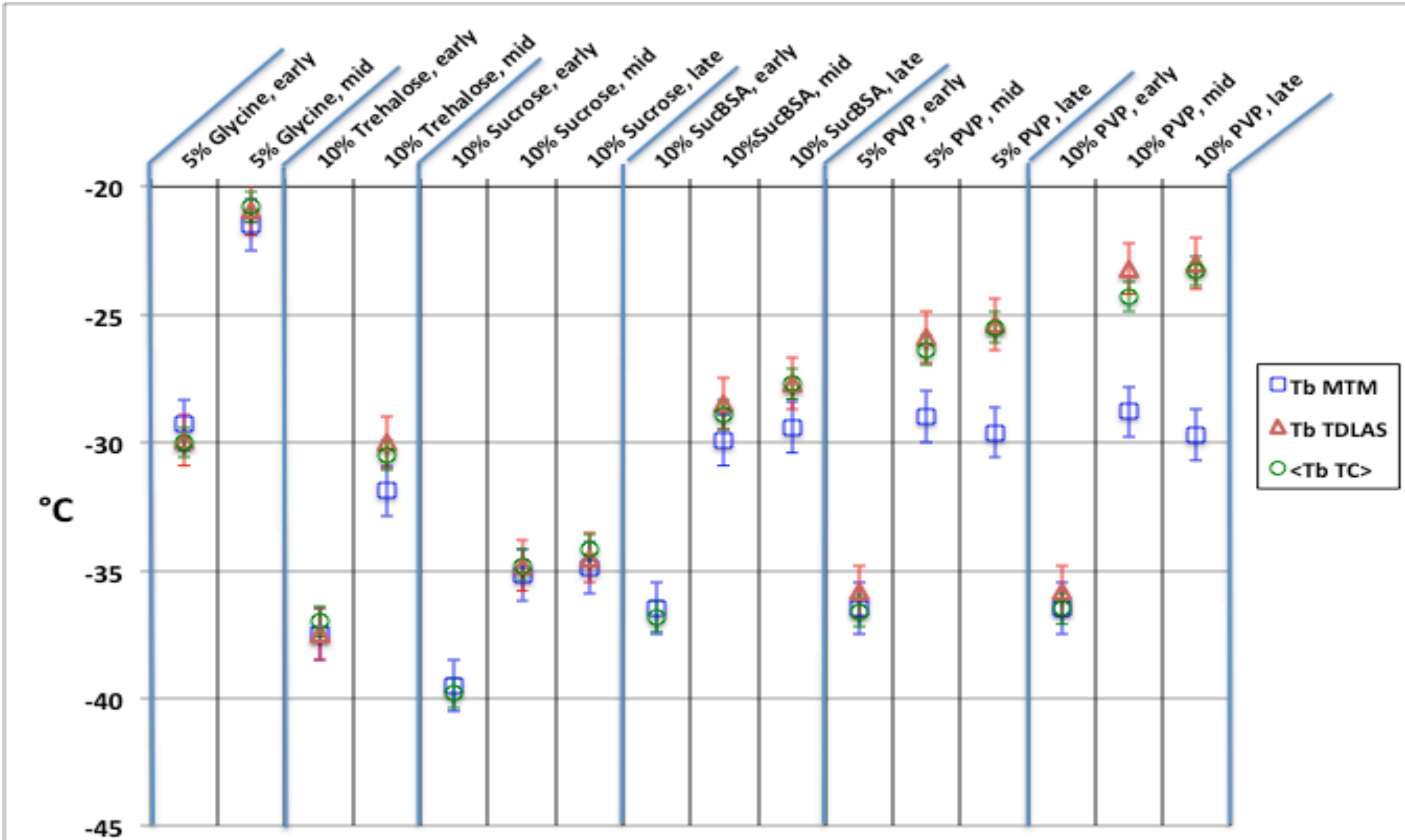
- **Expected errors modest**
  - **but need to be considered when comparing temperature data**

Experimental Setup



Comparison of T_b: MTM, TDLAS, TC avg

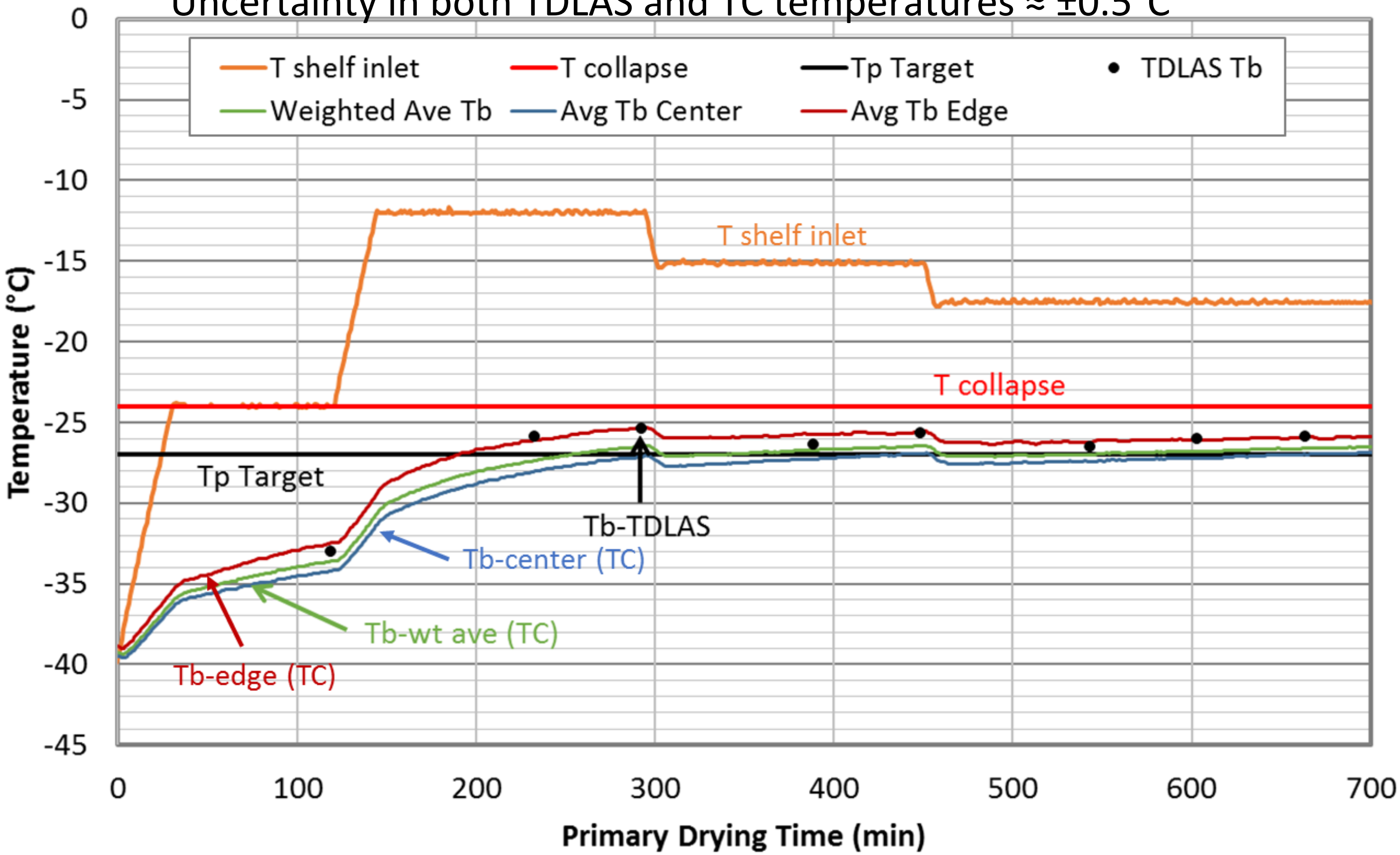
UConn Data: error bars are ±1°C for MTM and TDLAS and 0.8°C for Tc



- <u>Excellent agreement between TDLAS and Tc in all cases</u>
- **Good agreement between MTM and Tc for Glycine, acceptable for 10% sucrose, Trehalose, fair for BSA-Sucrose, but poor for PVP except for early data.**

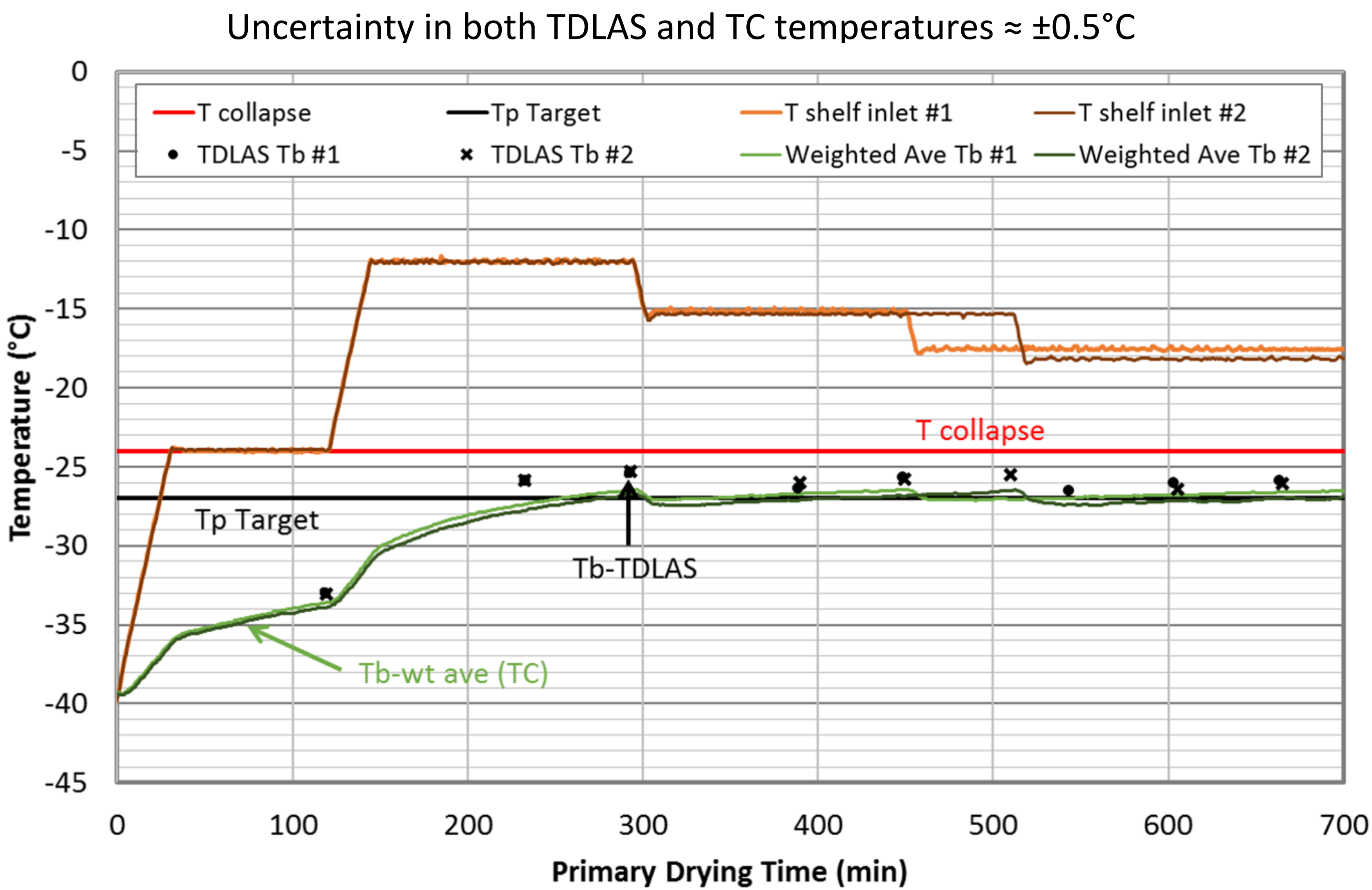
Example of TDLAS SMART FD Run on 10% PVP

Uncertainty in both TDLAS and TC temperatures ≈ ±0.5°C



- **Good agreement between TDLAS and TC temperatures**
- **Sensible cycle output from SMART: objective is Tb-TDLAS within ±1°C of Target once in control at ≈ 200 min**

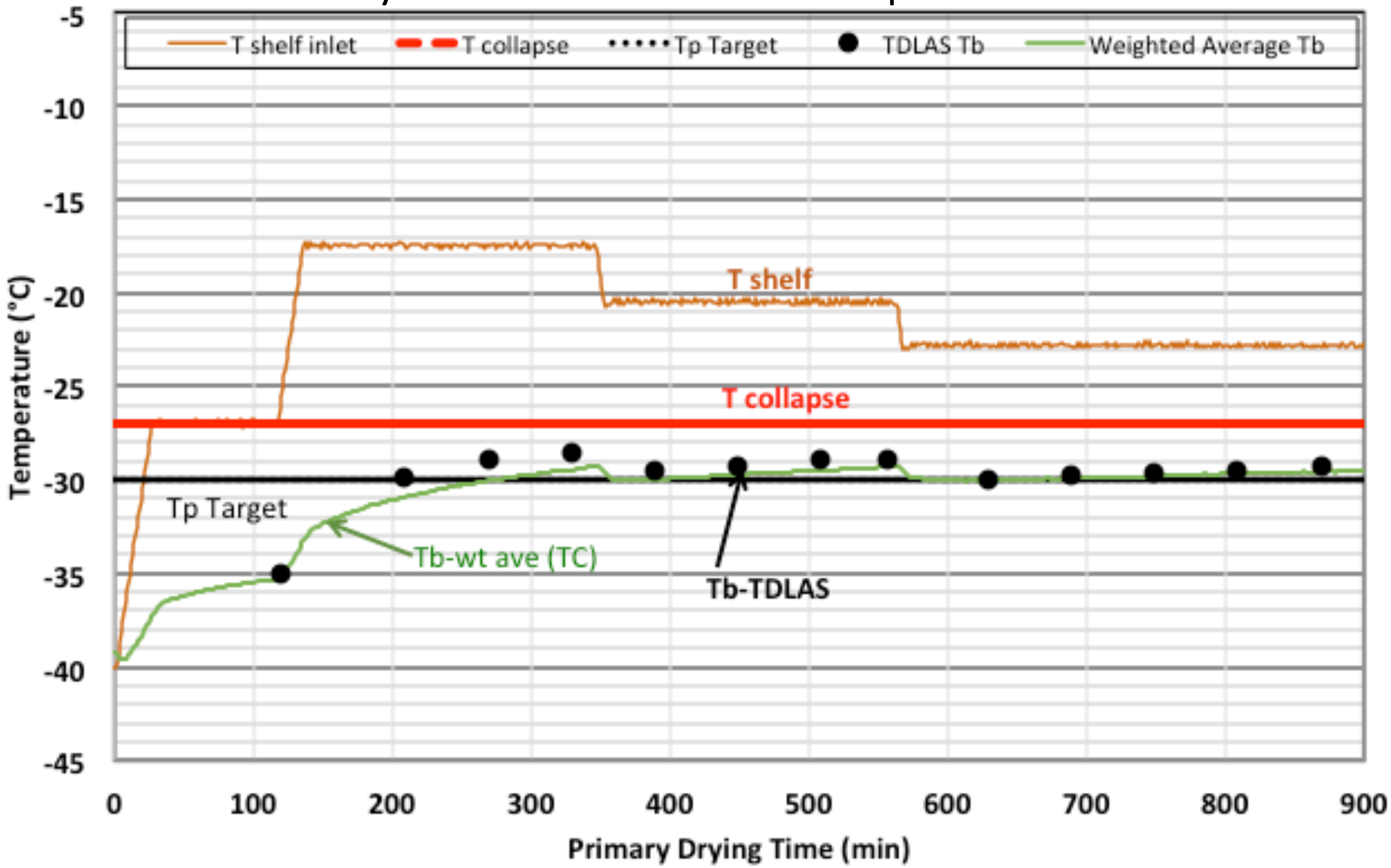
TDLAS SMART FD Run Repeatability: 10% PVP



- **Good agreement between two TDLAS SMART FD runs for 10% PVP**

TDLAS SMART FD Run on 10% Sucrose:BSA (1:1)

Uncertainty in both TDLAS and TC temperatures ≈ ±0.5°C



- **Good agreement between TDLAS and TC temperatures**
- **Sensible cycle output from SMART: objective is Tb-TDLAS within ±1°C of Target once in control at ≈ 200 min**

Summary & Conclusions

- Tunable Diode Laser Absorption Spectroscopy (TDLAS) is a noninvasive method to continuously measure the water vapor concentration and the vapor flow velocity and with a given value of vial heat transfer coefficient, can accurately measure product temperature over the full range of product drying.

- Product temperatures measured by TDLAS are accurate and in agreement with thermocouple data even when MTM fails badly due to the water-resorption phenomena.

- TDLAS sublimation rates and the calculated product temperatures can be combined with heat and mass transfer models of freeze drying to provide a SMART Freeze Drying procedure unencumbered by the inaccuracies of the MTM method.

- TDLAS is applicable to laboratory, pilot and production scale freeze dryers (process scale-up and process control), thus enabling a SMART freeze drying procedure in manufacturing.

Thank you!