Fundamentals of Freeze Drying

Lyo-Hub Summer School

Part 4 – Process Monitoring

Outline

- **Product temperature measurement**
  - **Why do we care?**
  - **Thermocouples**
  - **Resistance temperature detectors (RTD)**
  - **Wireless systems**
- **Pressure measurement**
  - **Thermal conductivity-type gauge**
  - **Capacitance manometer**

Outline (continued)

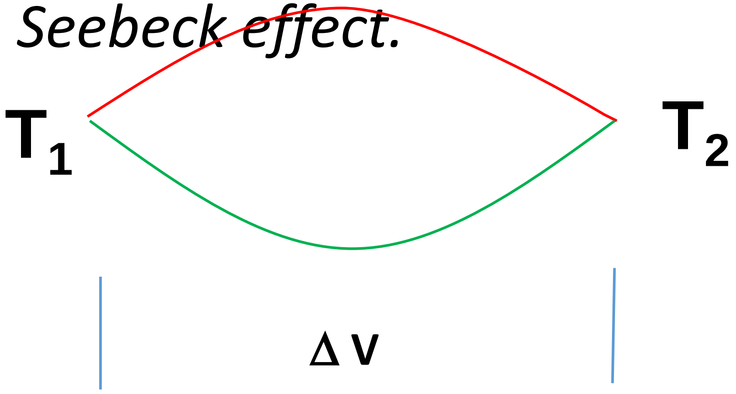
- Cycle Monitoring
    - Limitations of product temperature measurement
    - Alternatives to product temperature measurement for cycle end point detection
        - Comparative pressure measurement
        - Manometric temperature measurement
        - Pressure rise
        - Tunable diode laser absorption spectroscopy
        - Mass spectrometry
- Off-Line Methods
    - FM spectroscopy (Lighthouse)
    - AM spectroscopy (Bonfiglioli)

Why Do We Care About Product Temperature Measurement?

- Product temperature is the process variable that has the greatest potential impact on product quality (yet we don’t control it directly).
- Needed for laboratory scale development work
- Can be very useful at manufacturing scale for:
  - Scale-up studies
  - Validation
  - Transfers between manufacturing sites
  - Monitoring of routine production batches?

Types of Temperature Sensors

- Thermocouples
  - When two wires consisting of different metals are joined at the ends, and these ends, or *junctions*, are placed at two different temperatures, a voltage difference is generated between the junctions, and a current flows. This is known as the *Seebeck effect.*

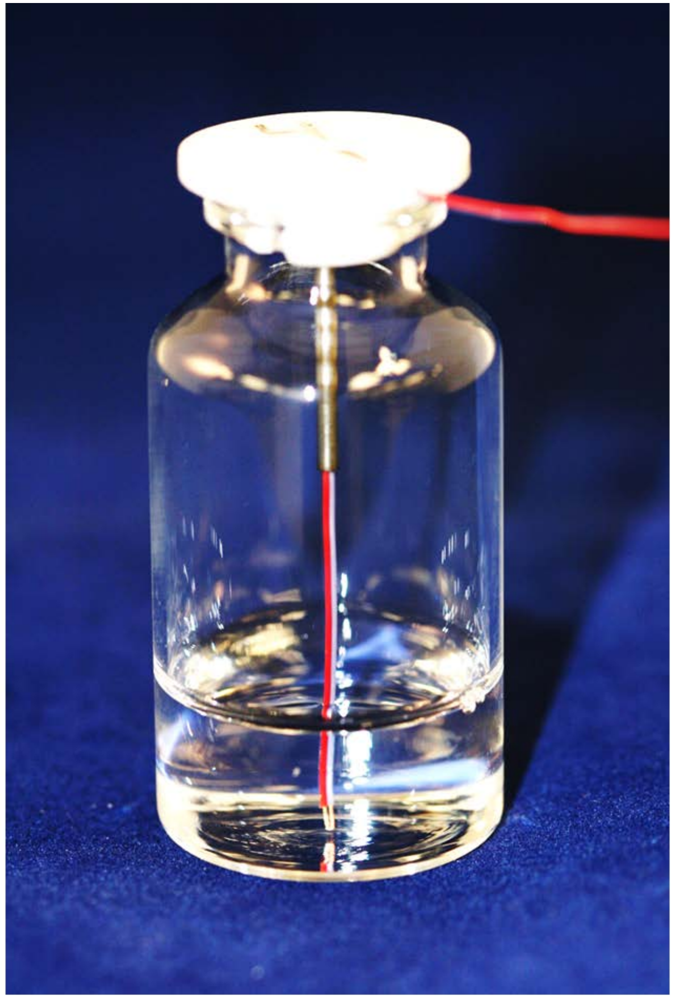


One junction is the *reference junction*, the other is the *measuring junction.* The reference junction can be a physical reference, like an ice bath or, more commonly, an electronic simulation of an ice bath.

Some Common Thermocouples

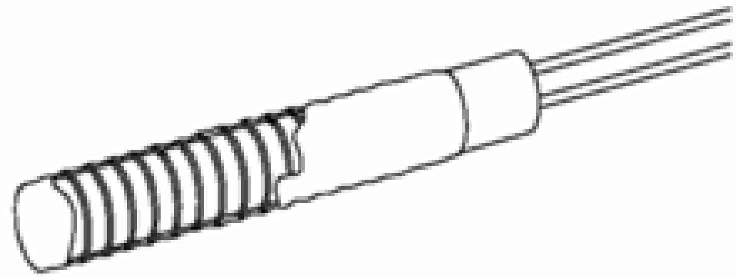
Type	Materials	Sensitivity (μV/deg K)	Comments
S	Platinum/Platinum + 10% Rhodium		Loses sensitivity at low temperature
T	Copper/constantan	43	Used in Lyo-Star lab freeze dryers
K	Chromel/alumel	41	Most common general-purpose TC
E	Chromel/constantan	68	Good for low temperatures
J	Iron/constantan	50	Lower limit about -40C

Pay Attention to Thermocouple Placement



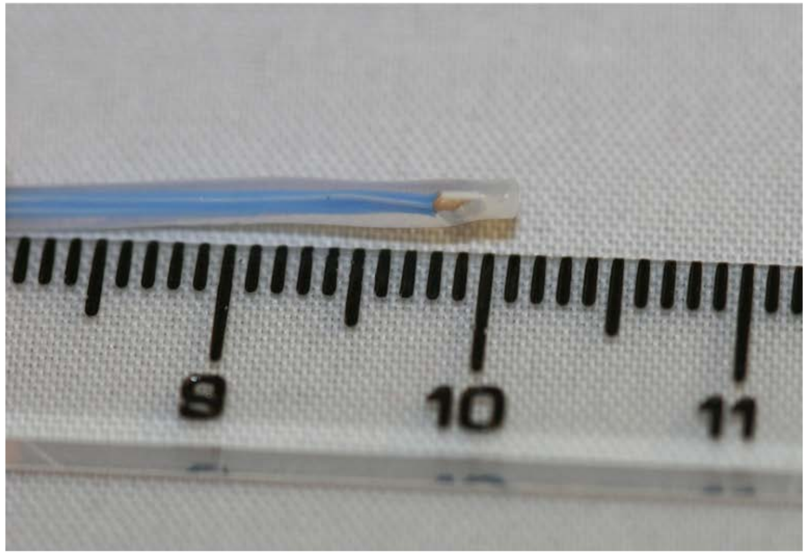
Types of Temperature Sensors

- Resistance Temperature Detectors (RTD)
  - Also called *resistance thermometer* or *resistance bulb*
  - The principle is that the resistance of a metal changes in a precise, linear way with temperature. Usually consist of a coil of fine wire (usually platinum, but may be copper or nickel) wrapped around a glass or ceramic core.



Product Temperature Measurement: RTDs

Product Temperature Measurement

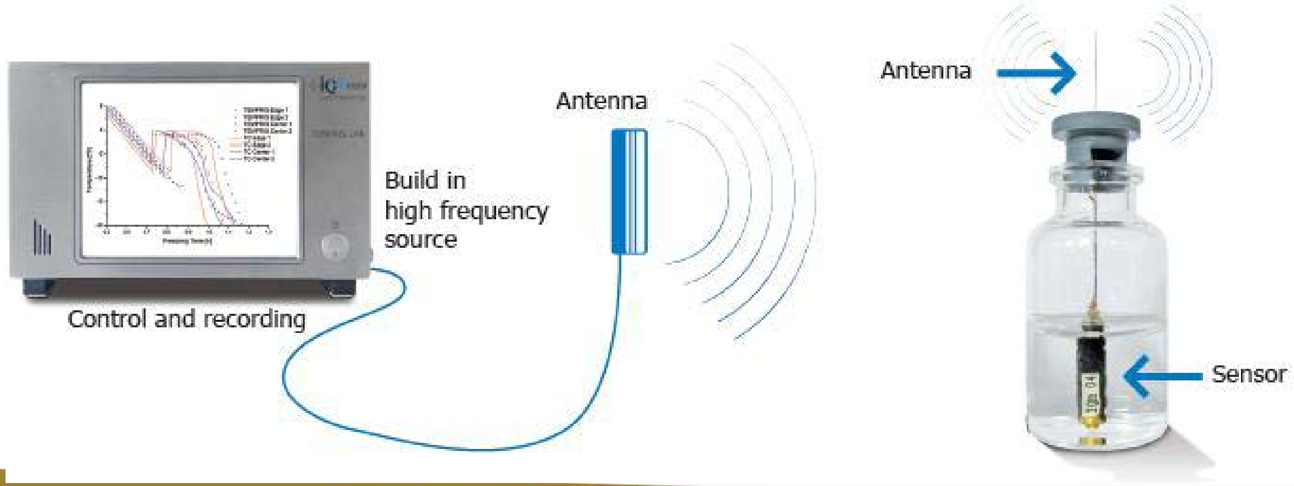


RTDs vs. Thermocouples

- RTDs are more accurate, more precise, more linear, and more stable (less drift) than thermocouples. All of the fixed temperature measurement points in our freeze drying systems are RTDs.
- The general advantages of thermocouples (useful at much higher temperatures, harsh environments, and faster response time) are not needed in freeze drying.
- We use thermocouples for product temperature measurement because a thermocouple reading is a measurement at a specific <u>point</u>, where the two wires are joined, and we want a point measurement of product temperature. RTD's, on the other hand, measure the average temperature over the surface of the sensor.

Tempris System

- Quartz based sensor operates by temperature dependent resonance.
  - Sensor is excited by modulated microwave signal
  - Oscillates in a temperature dependent frequency
  - Sensor response overlayed with the carrier signal leading to a frequency shift from which the product temperature is derived.

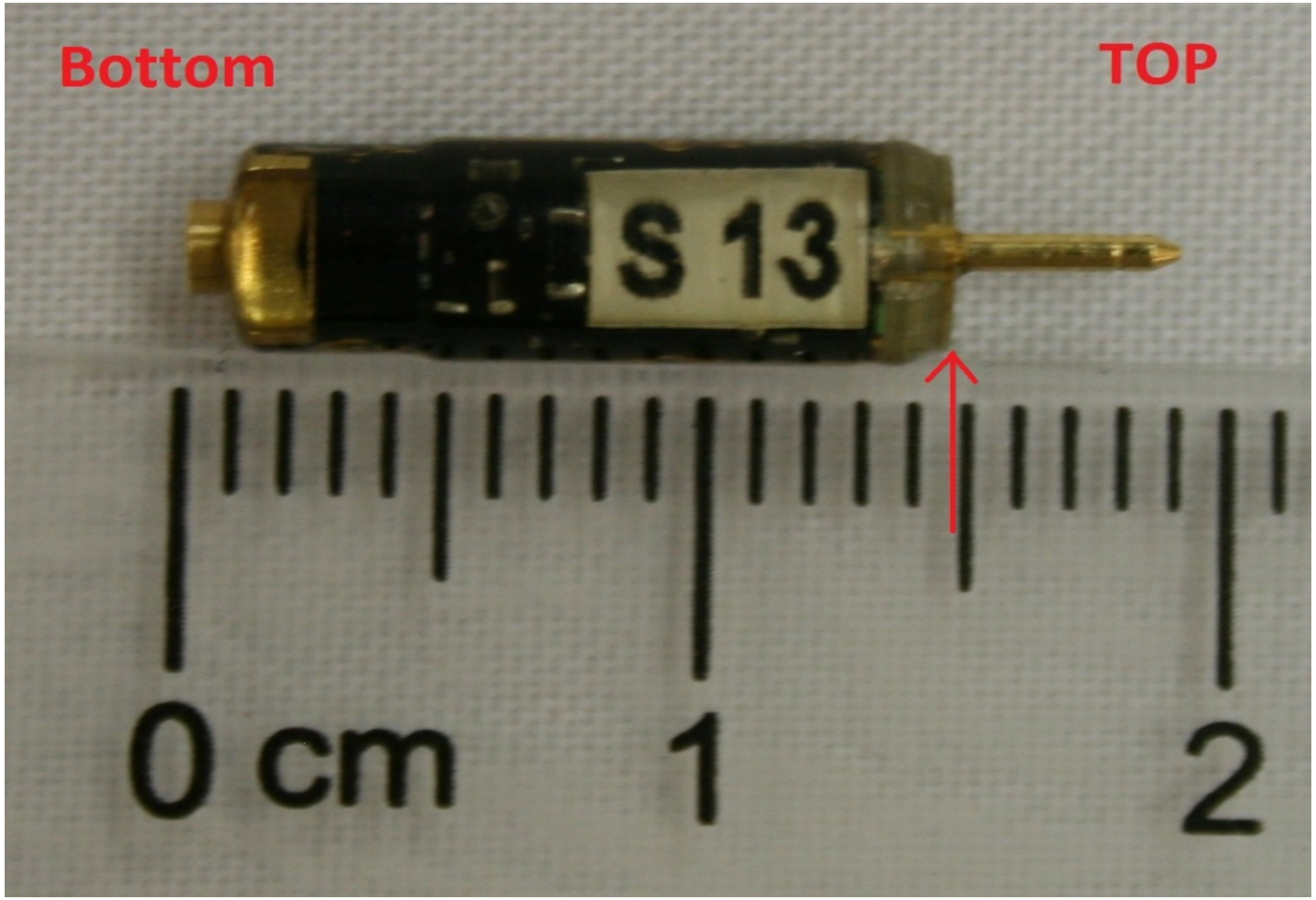


Tempris (continued)

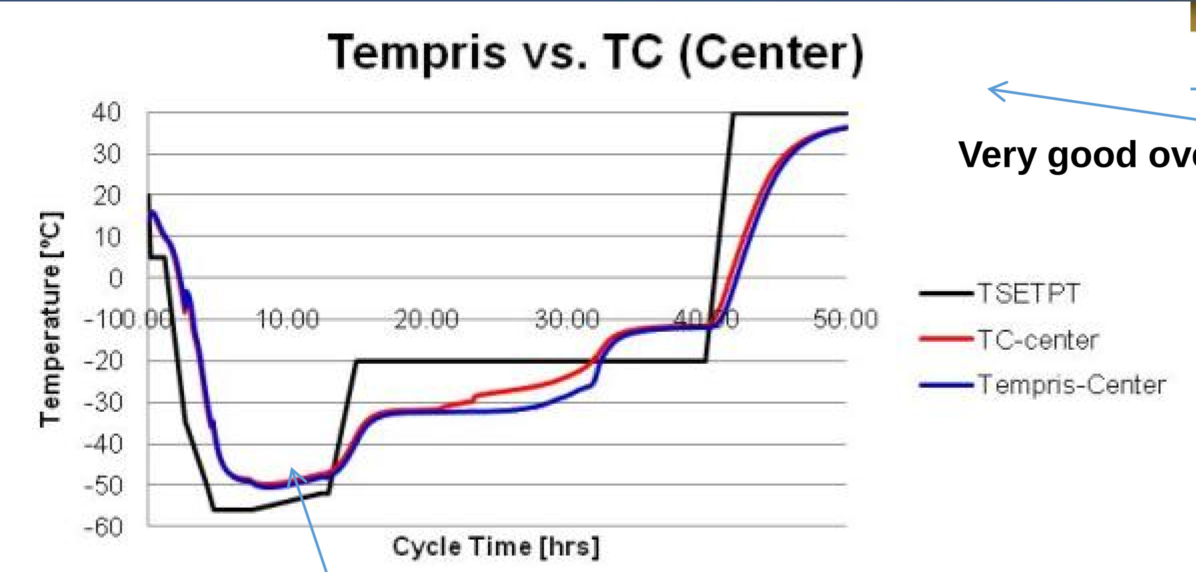
- All instrumentation is external to the freeze-dryer. Thus, there is no installation required, and the same instrument can be used for both laboratory scale and production scale equipment.
- The sensing element is relatively bulky compared to thermocouple or Ellab RTD. This can affect the depth of fill, particularly for small fills
- What about the “antenna” during stoppering?

Wireless Sensor in a Production Environment

Close-Up of Sensor

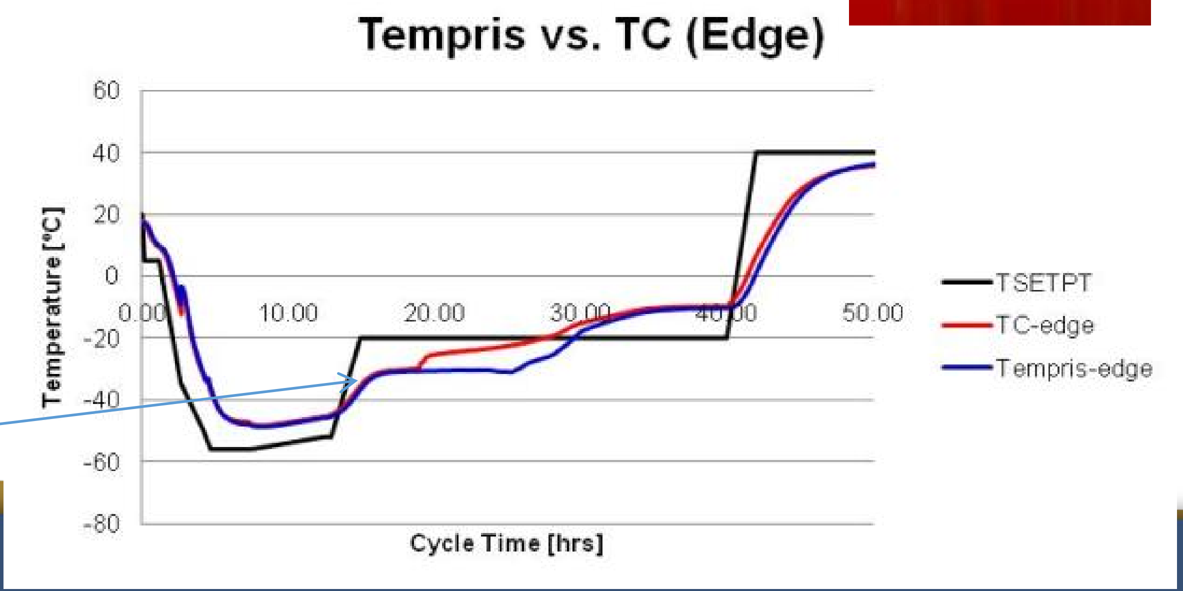


Tempris vs. Thermocouple in DCS



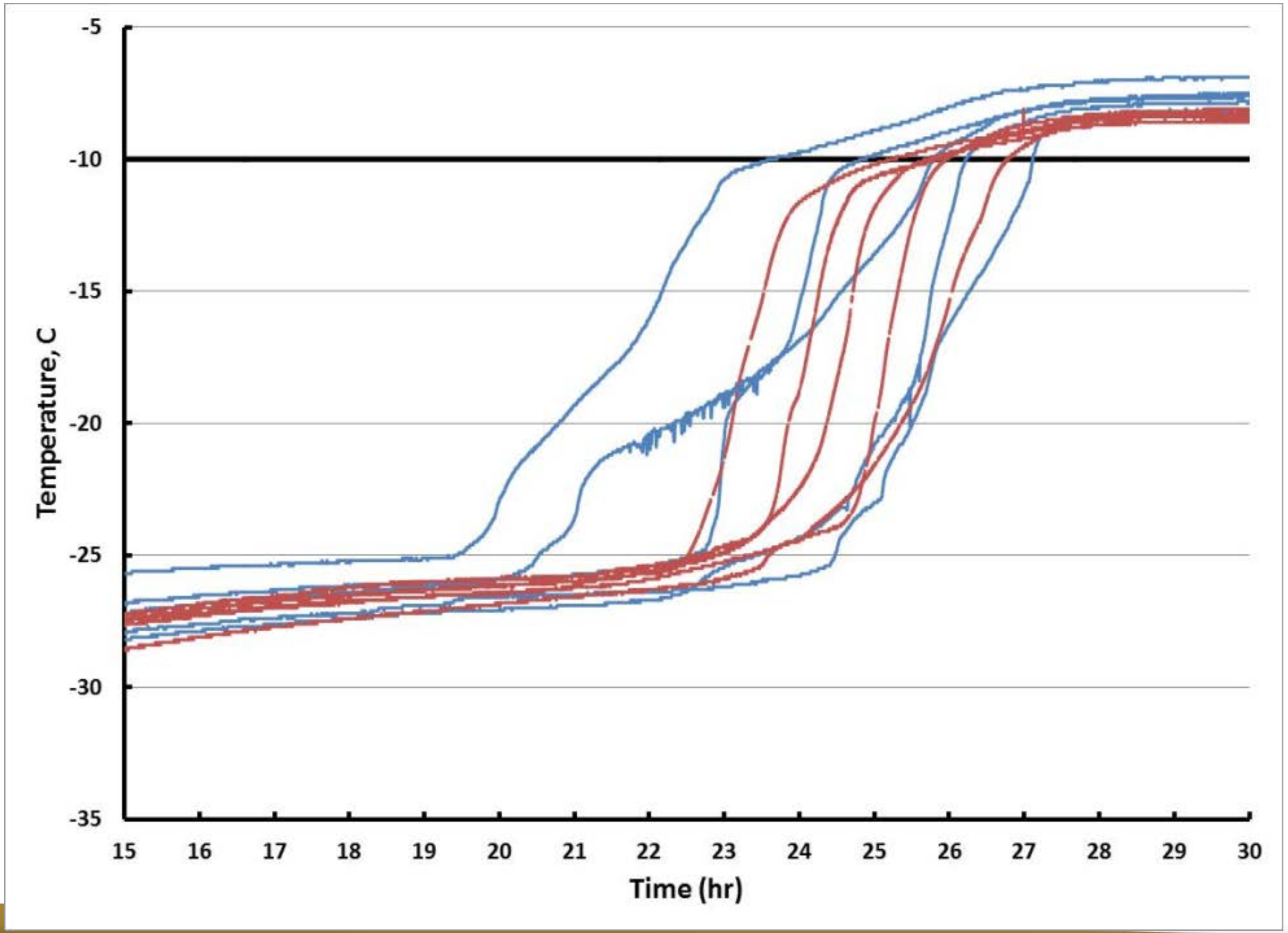
Very good overlay for SD

Excellent overlay for freezing



Excellent overlay for PD until
TC loses contact with ice

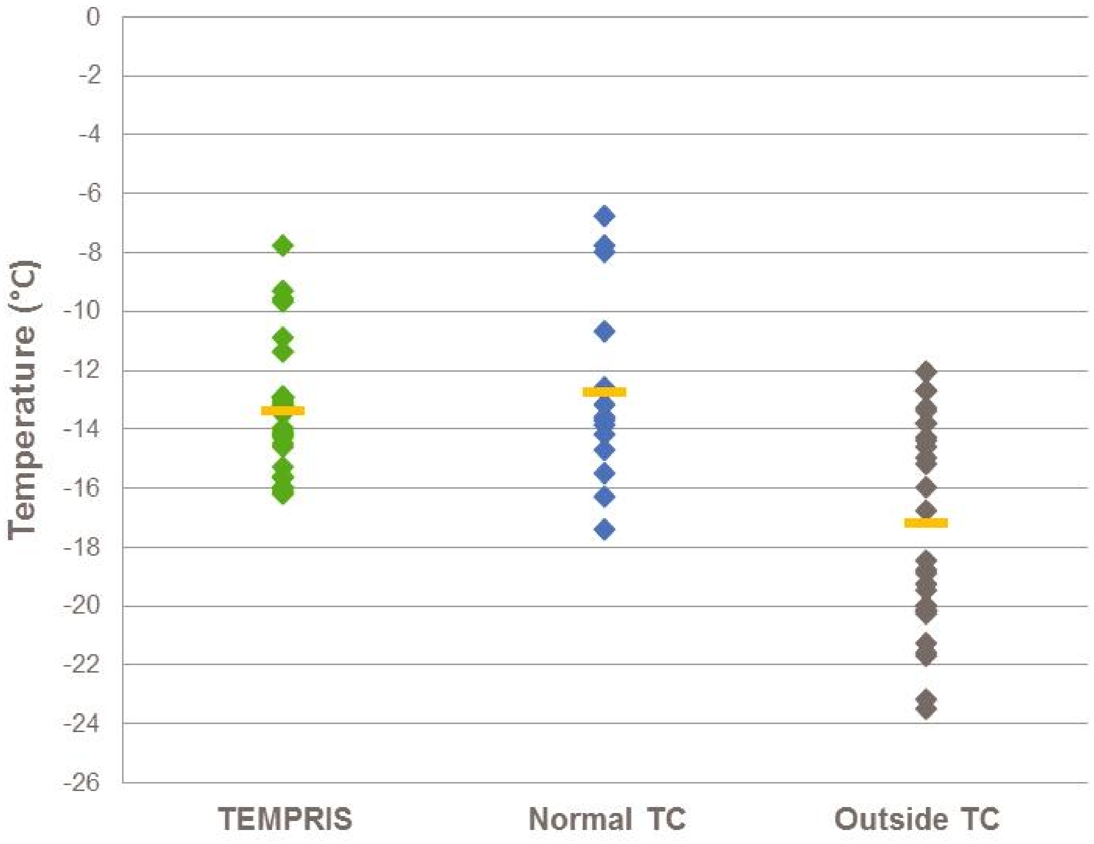
Process Data – Tempris vs. Thermocouples



Disadvantages of All Product Temperature Measurement Methods

- **Monitored vials are biased**
  - **supercool less**
  - **freeze slower**
  - **have larger average ice crystal size**
  - **freeze-dry faster than rest of batch (on average, about 10%)**
- **Must have a way of dealing with “bad” data**
- **Not compatible with automated material handling systems**
- **Compromise asepsis**

Influence of a Temperature Sensor on Ice Nucleation Temperature

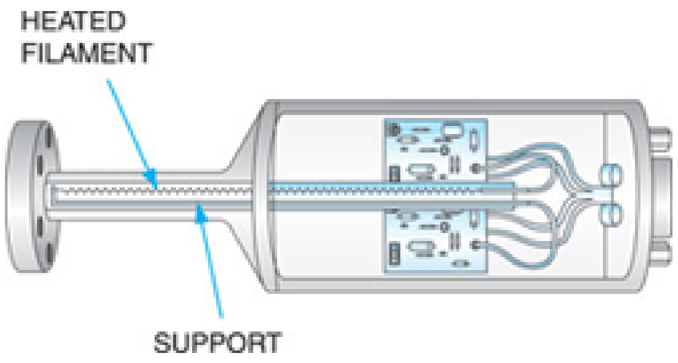


Pressure Measurement

- Thermal conductivity-type gauge
- Capacitance manometer

Pirani Gauge

In the Pirani gauge, two filaments are used as two "arms" of a wheatstone bridge. One filament is the reference filament, maintained at constant pressure and gas phase composition. The other filament is the measurement filament.



In the Pirani gauge, the filament temperature is controlled at a constant value. The Pirani gauge has about 100 times the range of a thermocouple gauge.

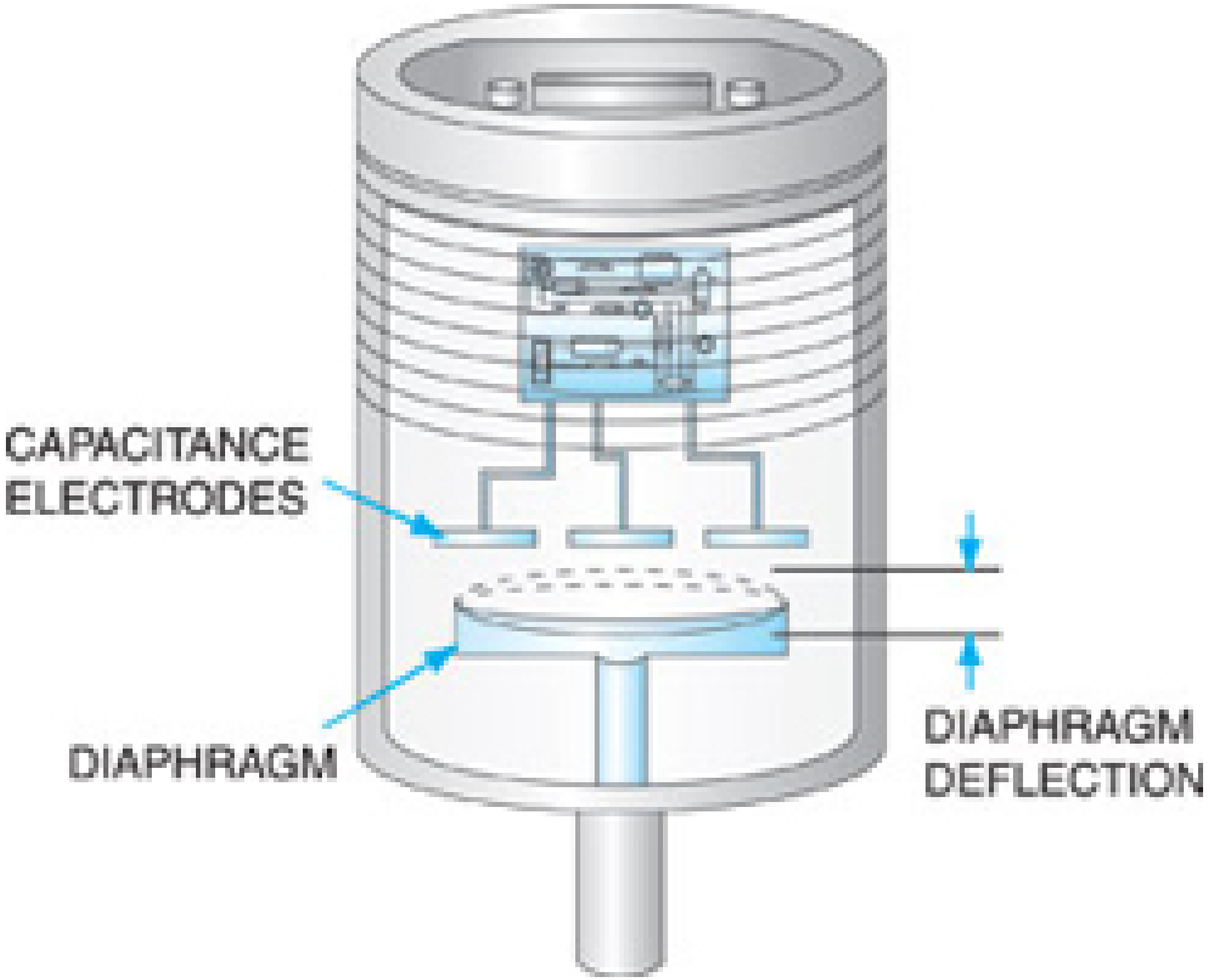
A Note about the Pirani Gauge and Organic Solvents

- Since both the thermocouple gauge and the Pirani gauge utilize a hot filament, the gauge must be turned off during freeze drying of formulations containing an organic co-solvent. Alternatively, some users flush the system with nitrogen before starting freezing.

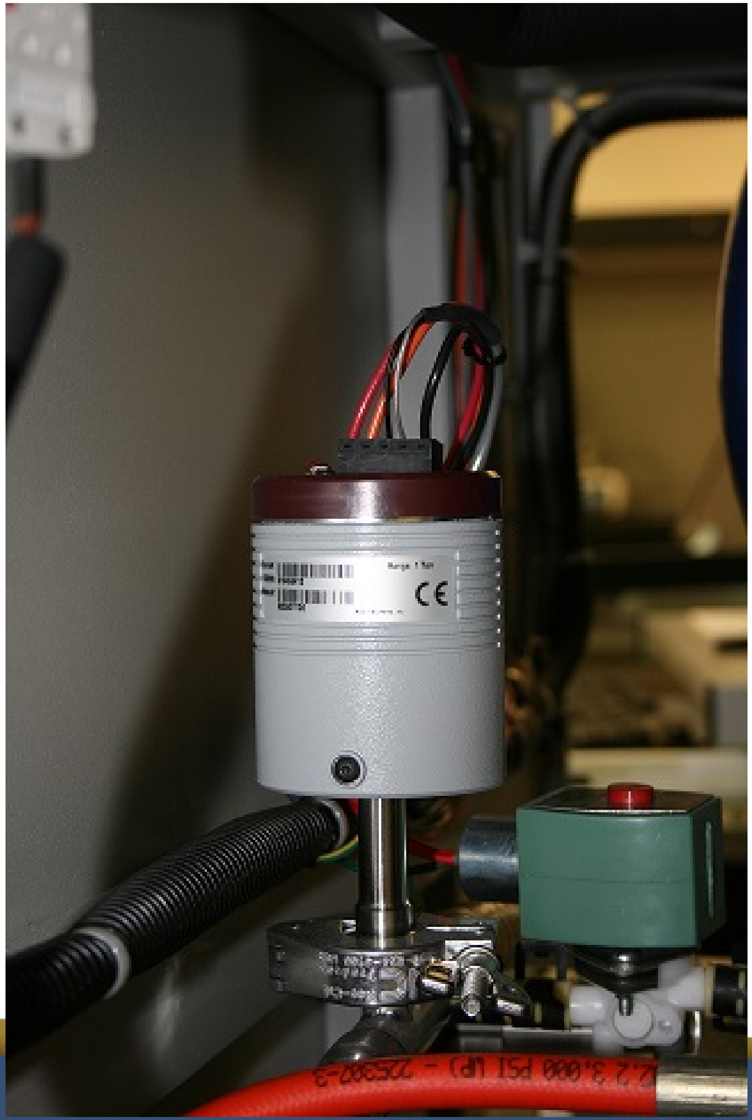
Thermal Conductivity-Type Gauge Accuracy Depends on:

- Constant gas phase composition
  - The composition of the vapor in a freeze dryer changes from essentially 100% water vapor during primary drying to essentially 100% nitrogen (or whatever the bleed gas is) during secondary drying.
  - We can use this characteristic to our advantage as a process monitoring tool.

Capacitance Manometer



Capacitance Manometer



Advantages of Capacitance Manometer

- Output is independent of gas phase composition
- Response is linear over 4 orders of magnitude

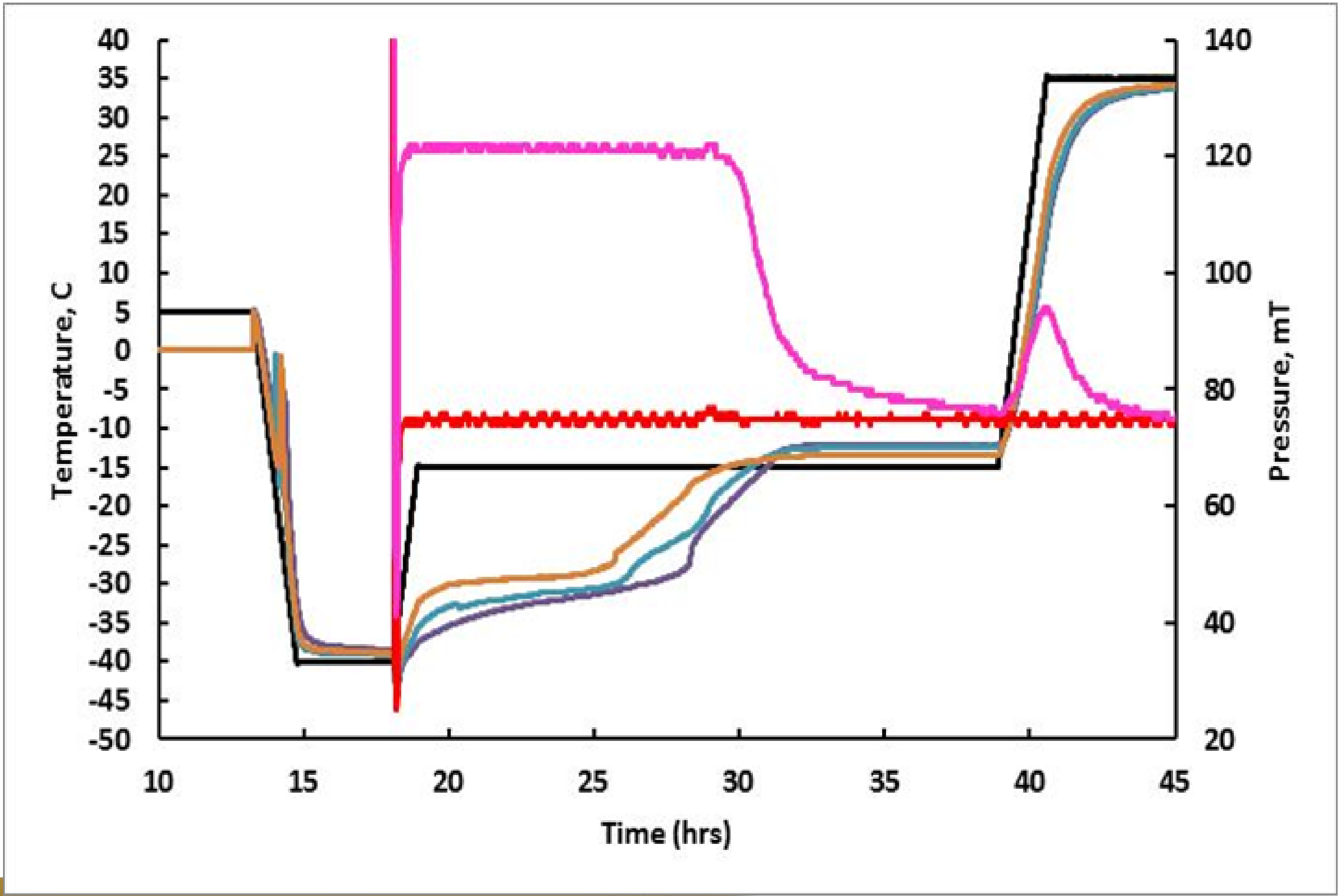
Alternatives to Product Temperature Monitoring

- Comparative Pressure Measurement
- Pressure Rise to Detect End of Cycle
- Mass Flow Meter on Gas Inlet Line
- Manometric Temperature Measurement (MTM)
- Tunable Diode Laser Absorption Spectroscopy (TDLAS)

Comparative Pressure Measurement

- Capacitance Manometer – Used to Monitor and Control Pressure in the Chamber
- Thermocouple-Type Gauge – Used for Monitoring Only

Example of Comparative Pressure Measurement



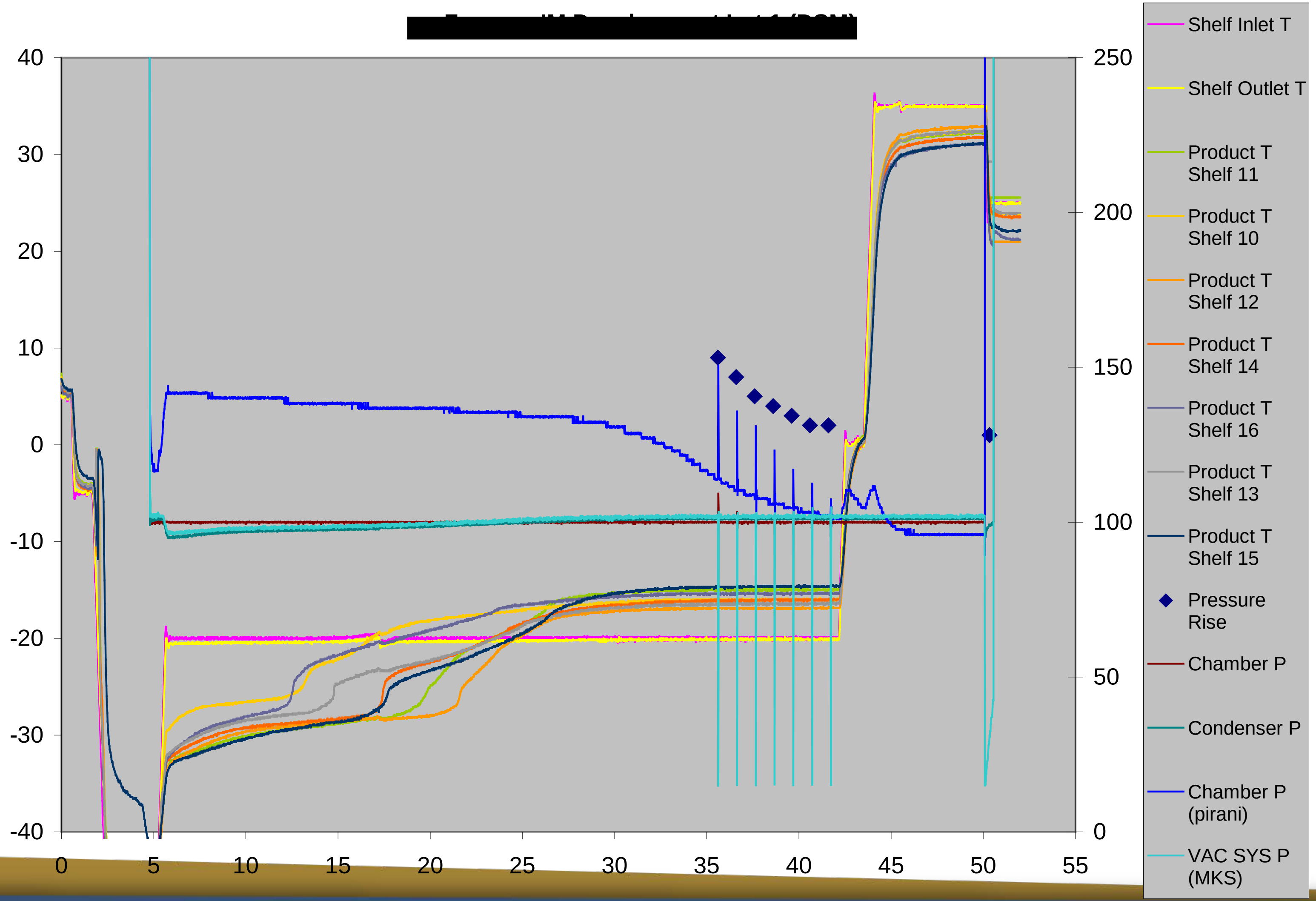
Advantages of Comparative Pressure Measurement

- It gives us information about the status of the product during freeze drying without the need for any type of sensors in individual vials.
- It's inexpensive, robust, and sensitive.
- It's useful for monitoring scale-up of cycles developed in lab scale equipment and transferred to production equipment.

Pressure Rise

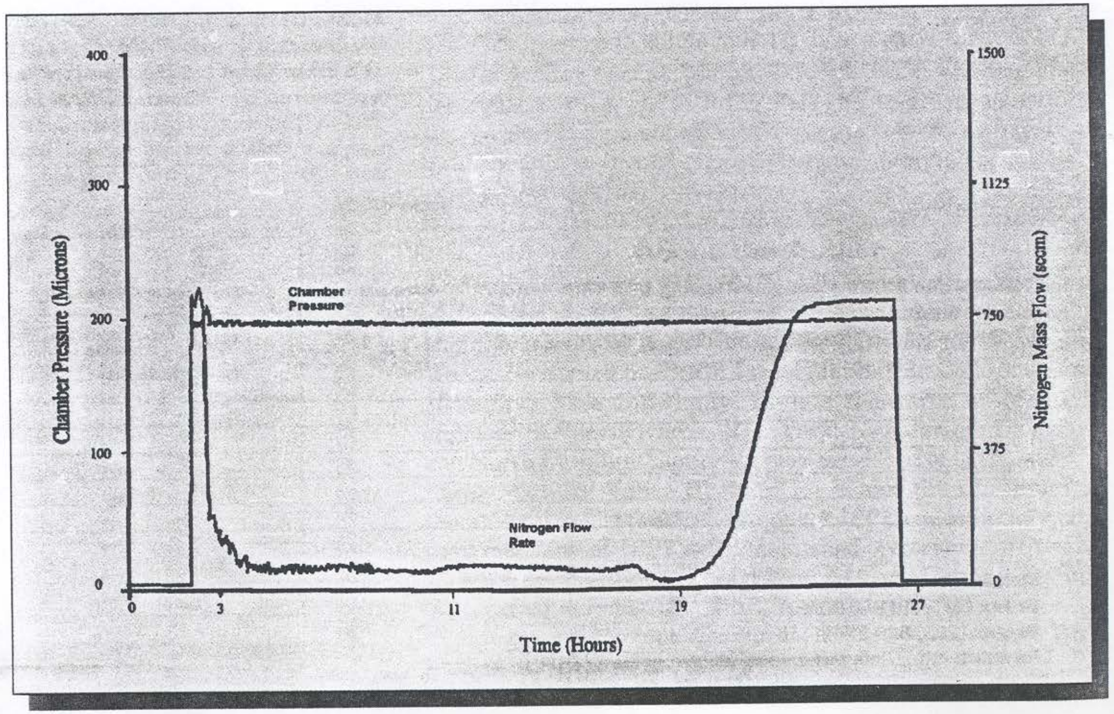
- Used generally to determine end point of drying.
- Based on closing the valve between the chamber and the condenser briefly near the end of drying and monitoring chamber pressure. When no more water vapor is being evolved from the product, the cycle is finished
- This technique assumes a low, and approximately constant, background leak rate.

Pressure Rise Data



Mass Flow Meter on Gas Bleed Line

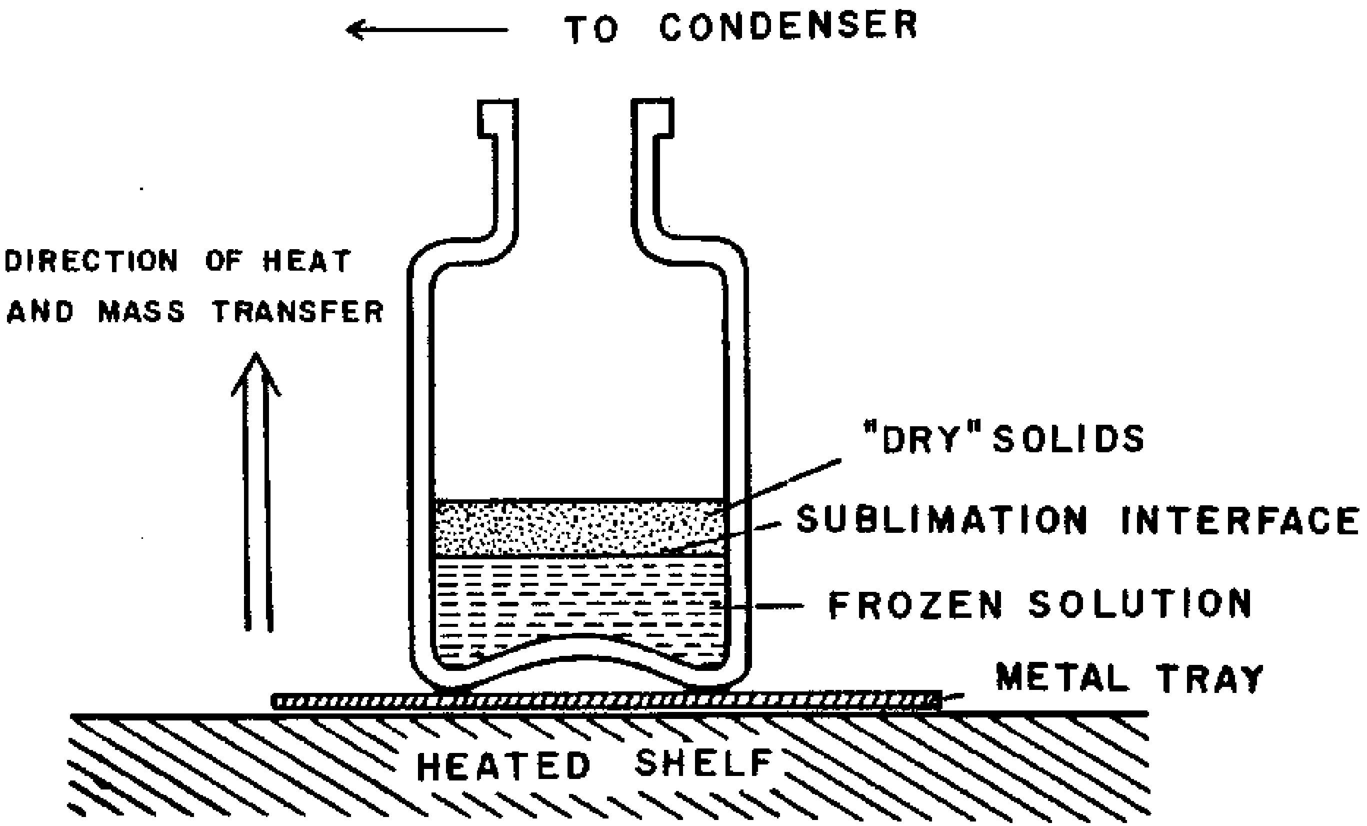
Figure 1. Response of nitrogen flow during lyophilization.



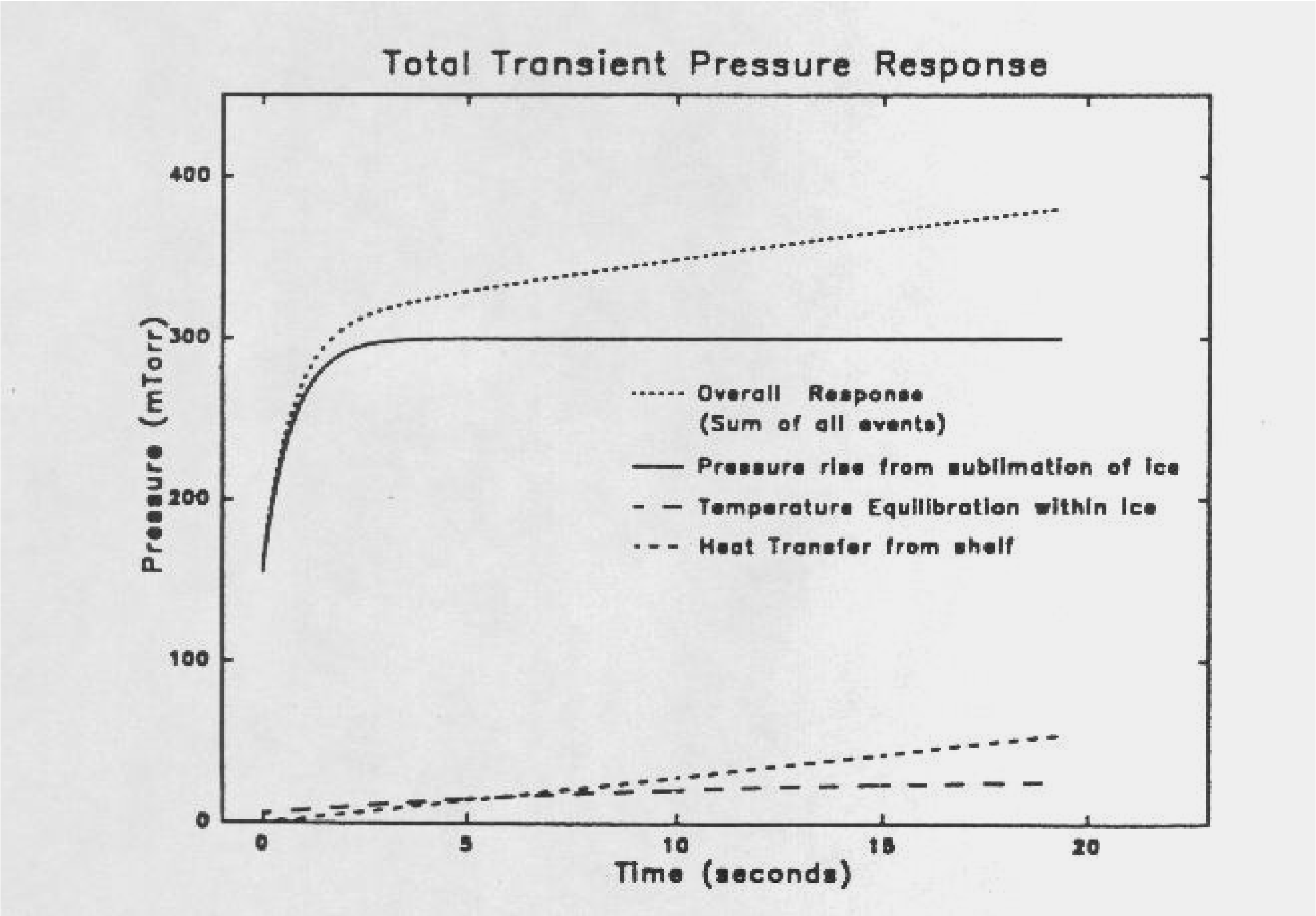
Manometric Temperature Measurement

Manometric temperature measurement is developing technology for measuring product temperature without using temperature probes. It consists of measuring the transient pressure response when the valve between the chamber and condenser is closed during primary drying. The technique also allows measurment of product resistance to mass transfer and the vial heat transfer coefficient.

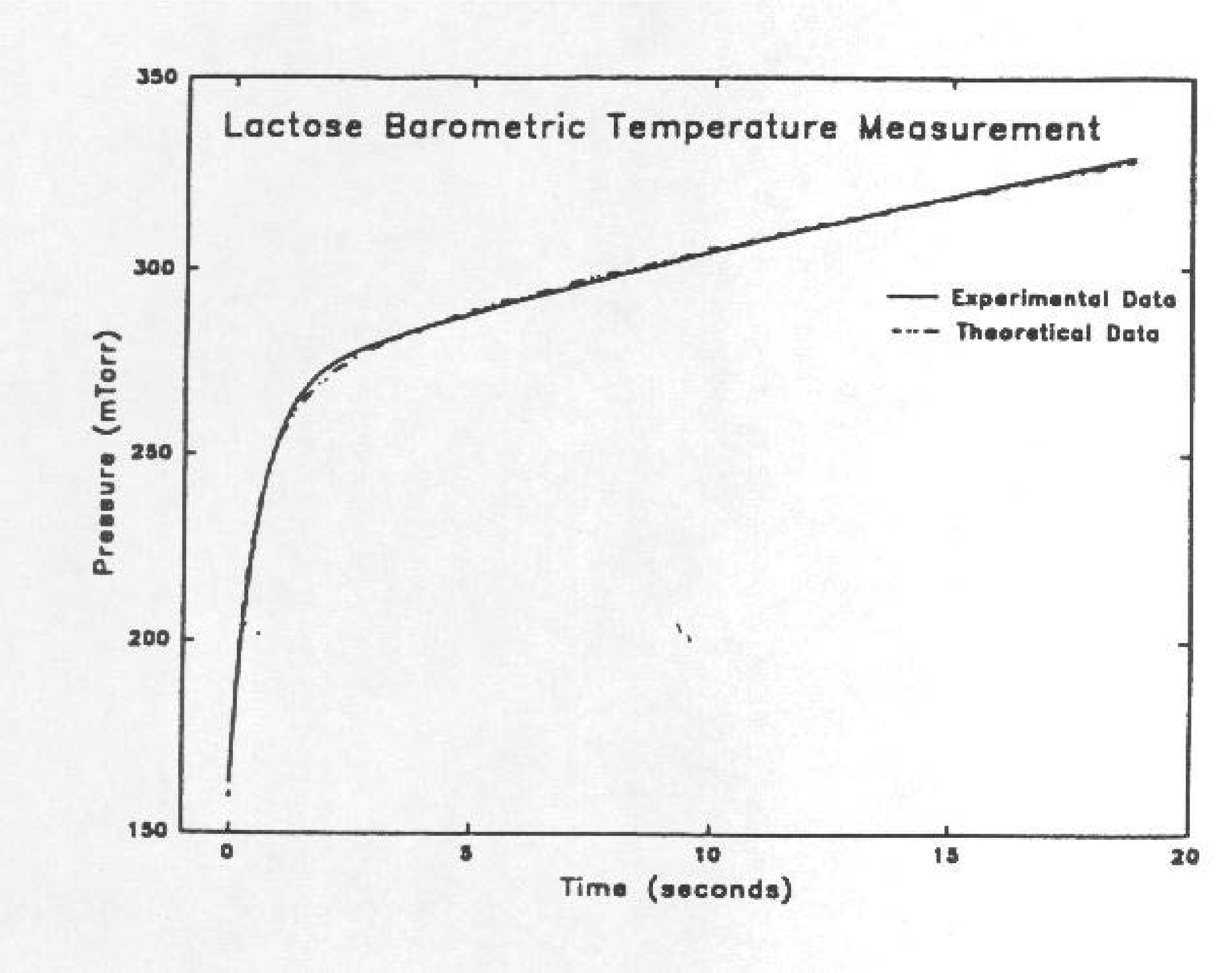
Heat and Mass Transfer in Freeze-Drying



Total Transient Pressure Response (calculated)



Experimental vs. Theoretical Response



Manometric Measurements Give:

- **Product temperature**
  - Agreement between MTM and temperature probes is reasonable given the differences in position of the measurement - MTM give sublimation front temperature and temperature probe gives temp at position of probe. MTM temperature biased toward coldest vials
- **Product resistance to mass transfer**
  - Can detect collapse of product by these measurements. Values by MTM tend to be lower than “actual” values because of product temperature heterogeneity
- **Vial heat transfer coefficient**
  - There is a better way than MTM to do this.
- **Sublimation Rate**

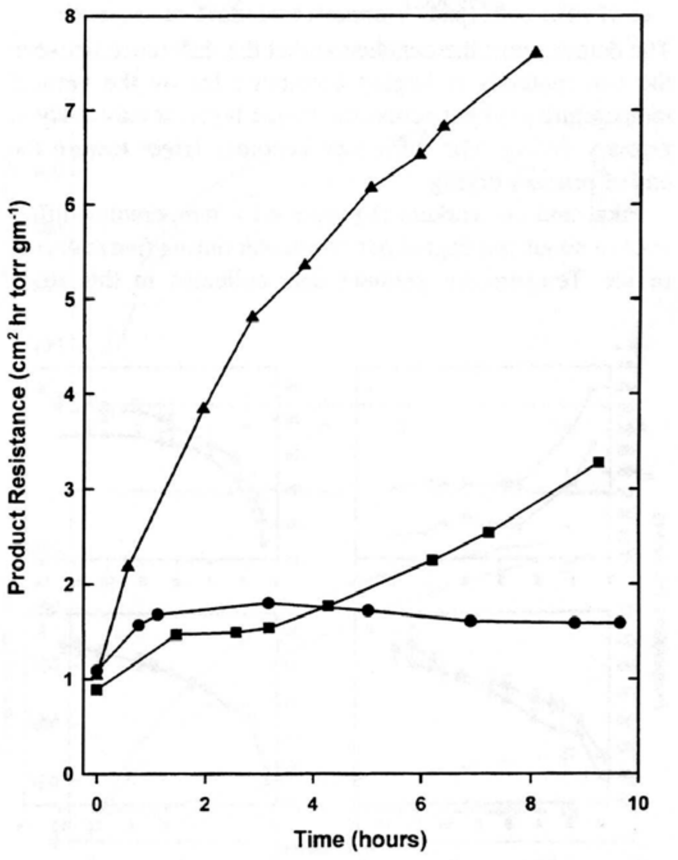
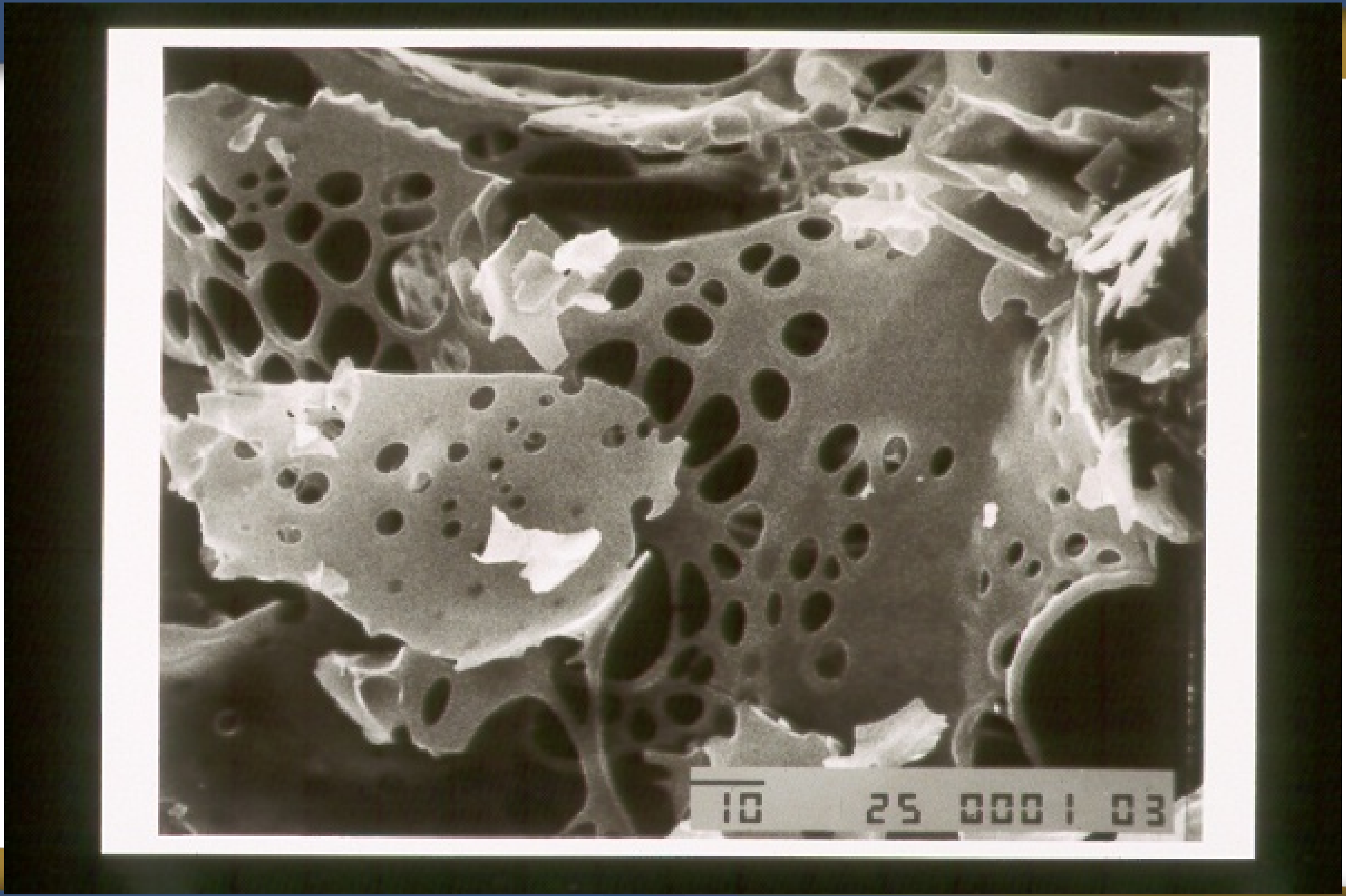


Figure 6—Area normalized product resistance during the freeze drying of 5% w/v mannitol (triangles), 5% w/v potassium chloride (squares) and 5% w/v lactose (circles) solutions at a shelf temperature of 0°C and chamber pressure of 100 millitorr.


10
25 0003 03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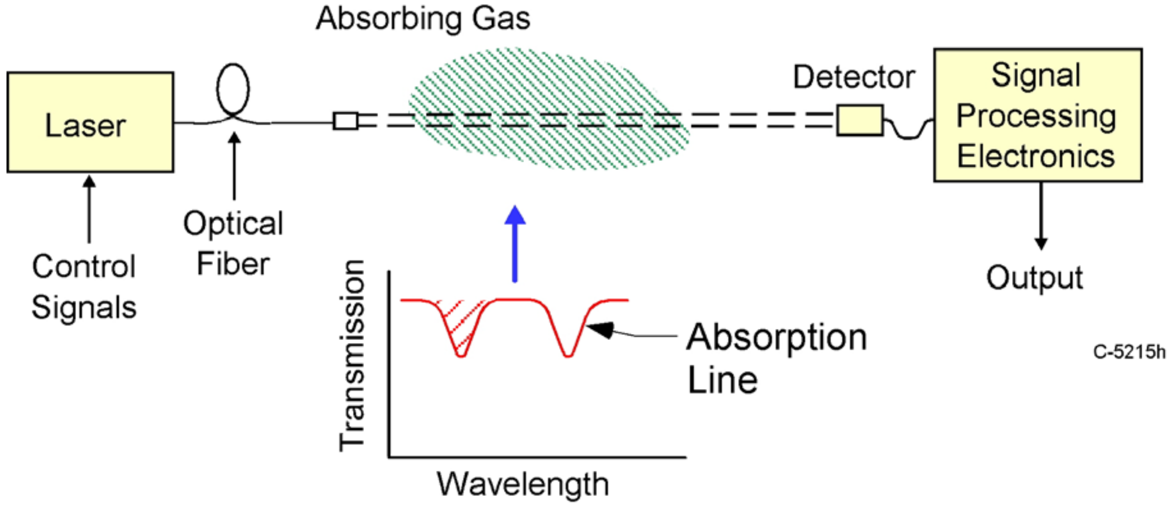
The “Smart Freeze-Dryer”

The “Smart Freeze Dryer” is based on manometric temperature measurement, and uses an algorithm where the user enters the product temperature to be maintained during primary drying. The algorithm then manipulates the set point of the shelf temperature in order to reach this product temperature. The advantage of this approach is that it minimizes the amount of trial and error work needed to optimize a cycle, even by personnel who are not experts in the subject.

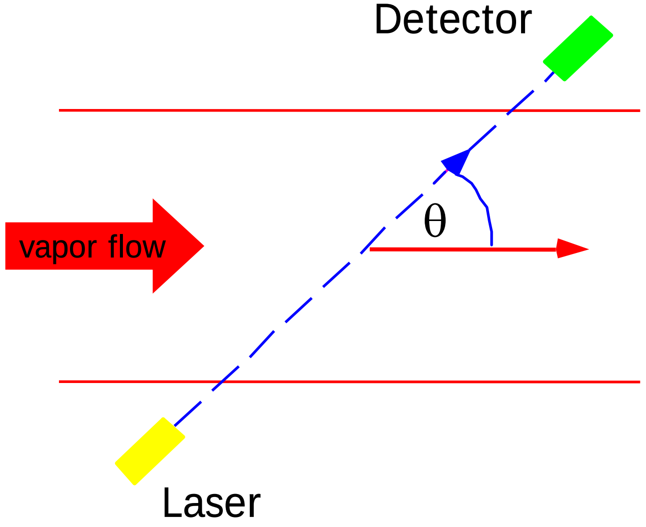
Tunable Diode Laser Absorption Spectroscopy (TDLAS) Mass Flux Measurements

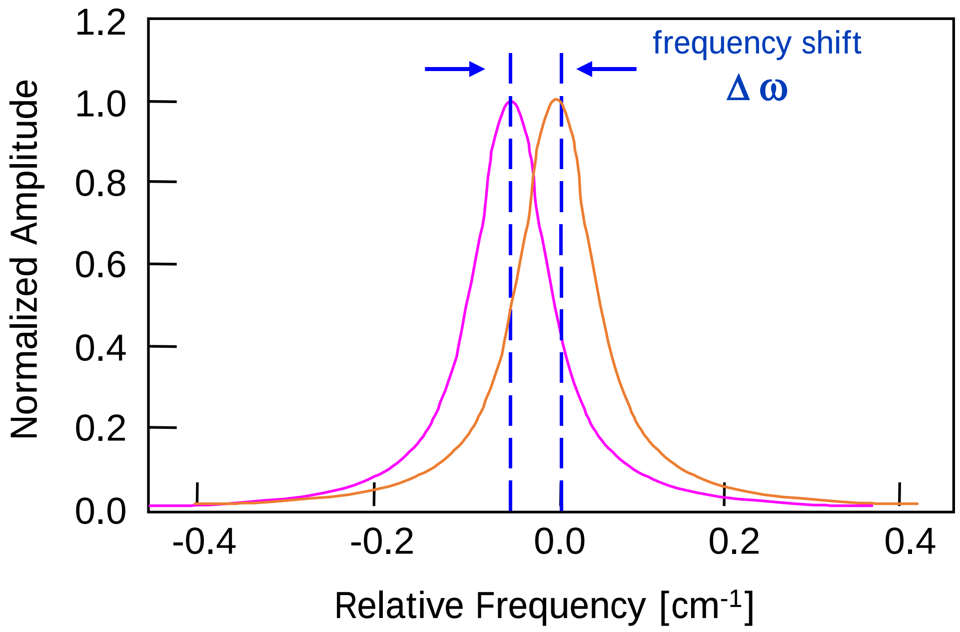
- Optically measure water vapor concentration
- Optically measure gas velocity
- Use the concentration and velocity measurements to determine the water vapor removal rate from the product vials (grams/second)
- Integrate the water removal rate during the process to predict the total amount of water removed (mass balance)

Slide courtesy of Bill Kessler, Physical Sciences, Inc., Andover, MA



Measurement Principles – Basic Physics I





density

$$\rho = \frac{\int_0^{\omega} \ln(I / I_o)\, d\omega}{S \ell} \quad [g/cm^3]$$

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

velocity

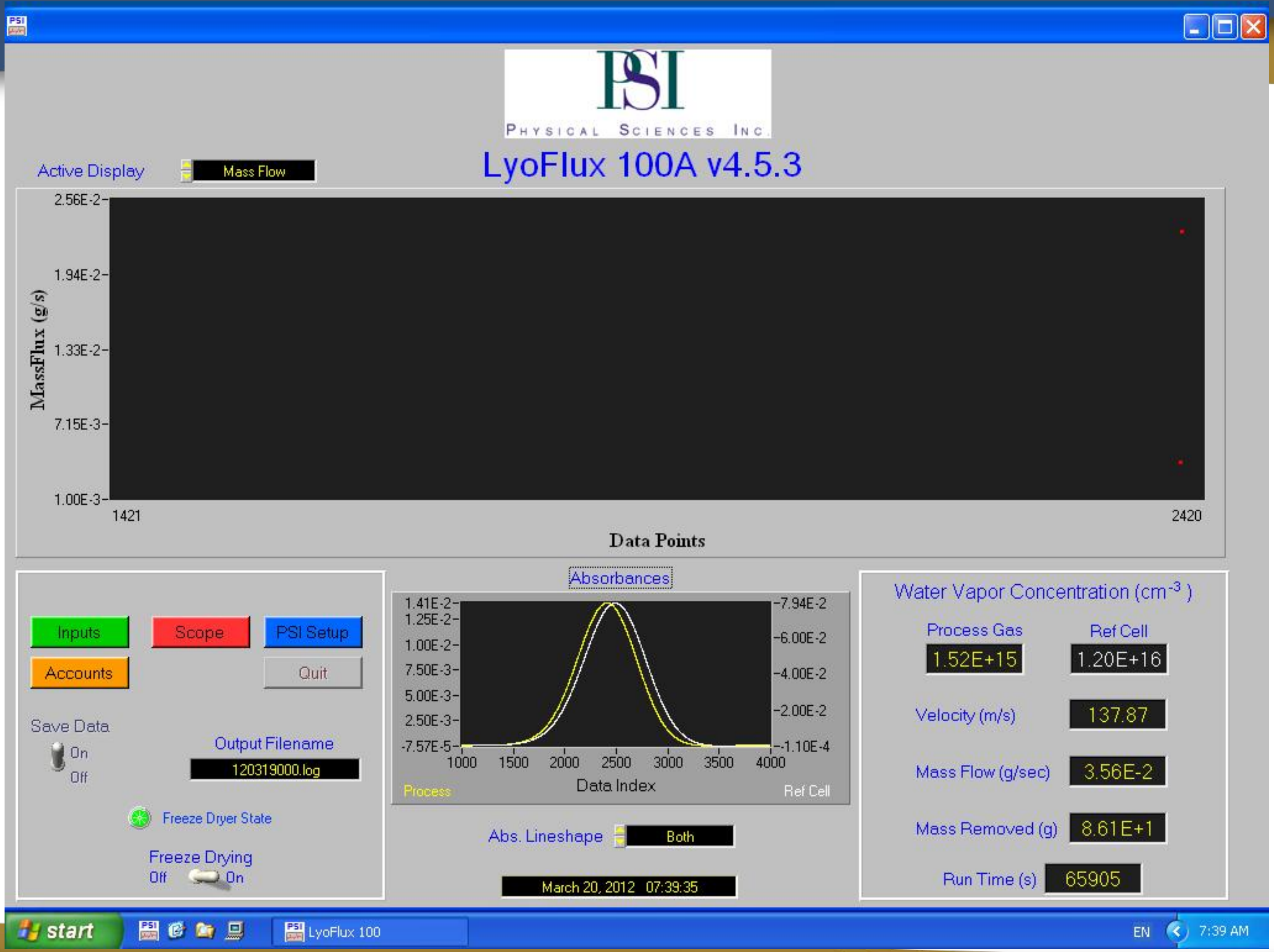
$$u = \frac{\Delta\omega\, c}{\omega_o\,(\cos\theta_1 - \cos\theta_2)} \quad [cm/s]$$

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

mass flux

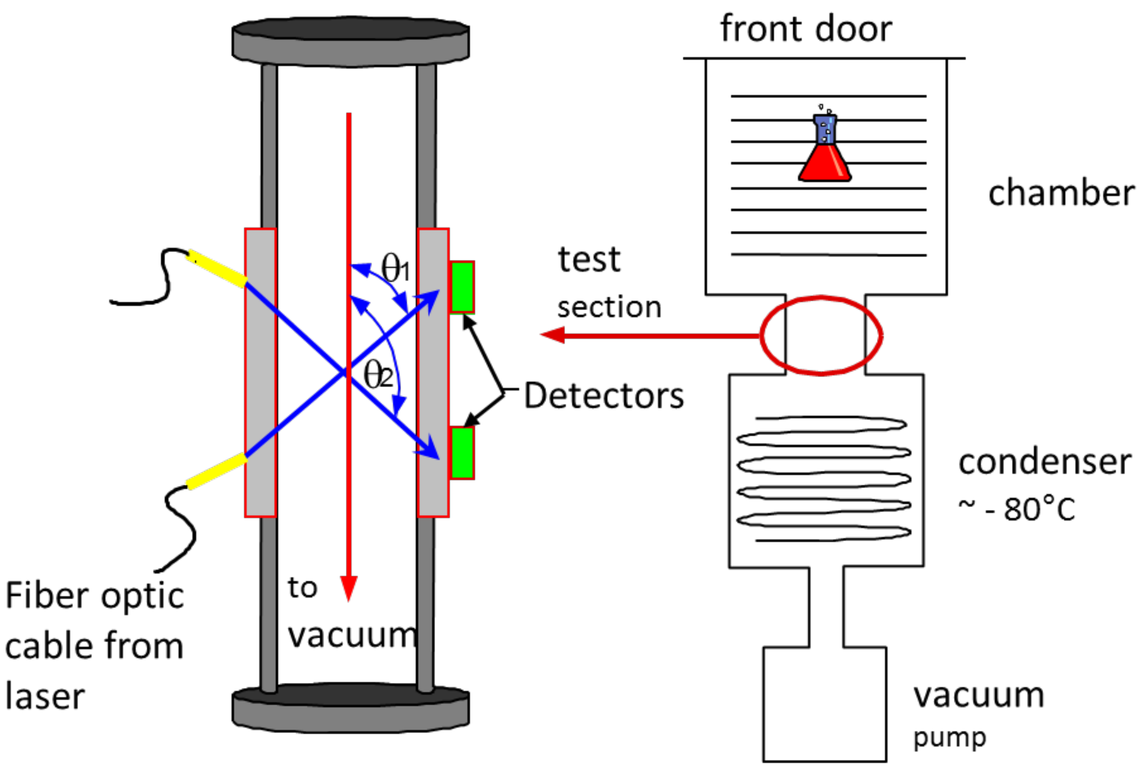
$$dm / dt = u \cdot \rho \cdot A \quad [g/s]$$

Determined using velocity, density and duct cross-sectional area

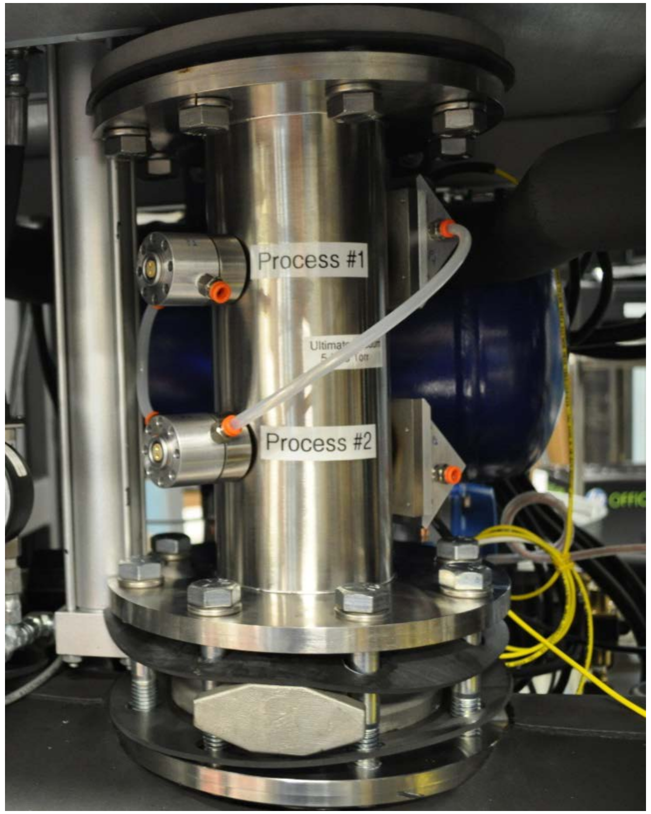


PHYSICAL SCIENCES INC.
LyoFlux 100A v4.5.3
Active Display
Mass Flow
MassFlux (g/s)
2.56E-2
1.94E-2
1.33E-2
7.15E-3
1.00E-3
1421
2420
Data Points
Inputs
Scope
PSI Setup
Accounts
Quit
Save Data
On
Off
Output Filename
120319000.log
Freeze Dryer State
Freeze Drying
Off
On
Absorbances
Data Index
Process
Ref Cell
Abs. Lineshape
Both
March 20, 2012 07:39:35
Water Vapor Concentration (cm-3)
Process Gas
Ref Cell
1.52E+15
1.20E+16
Velocity (m/s)
137.87
Mass Flow (g/sec)
3.56E-2
Mass Removed (g)
8.61E+1
Run Time (s)
65905
start
LyoFlux 100
EN
7:39 AM

Tunable Diode Laser Absorption Spectroscopy (TDLAS)

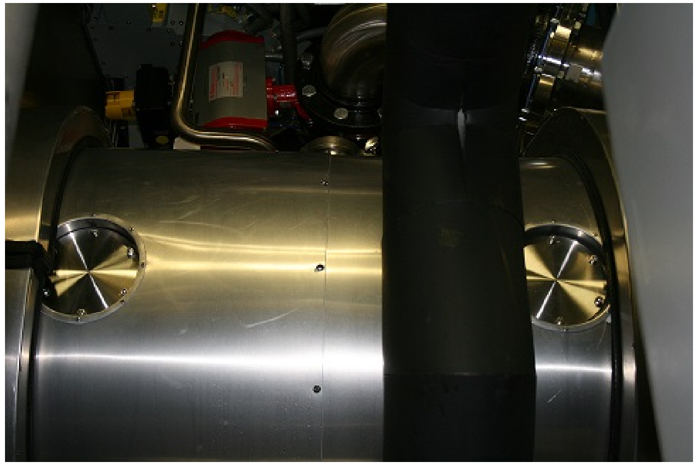


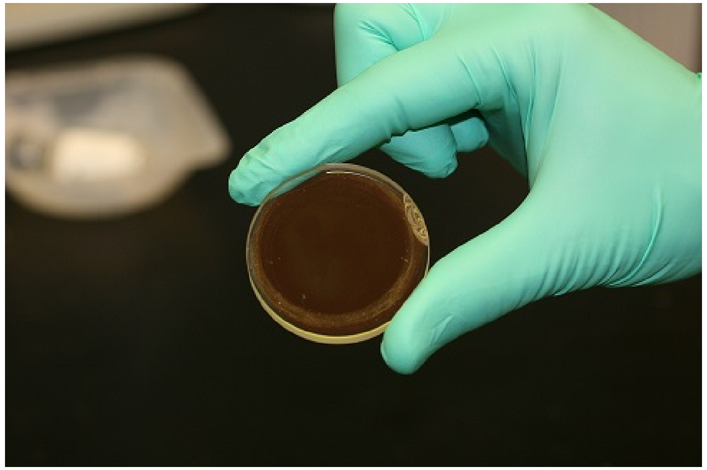
LyoFlux 100 Optical Spool

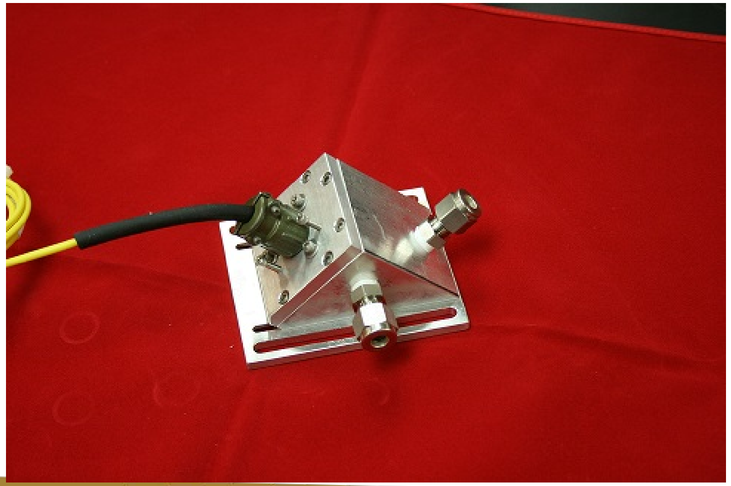


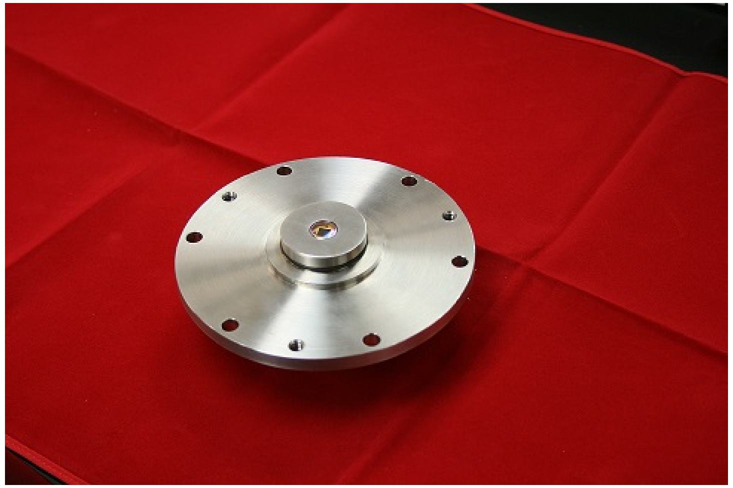
LyoFlux 200 Optical Spool
Installed in a Lyostar III lyophilizer

TDLAS at Manufacturing Scale

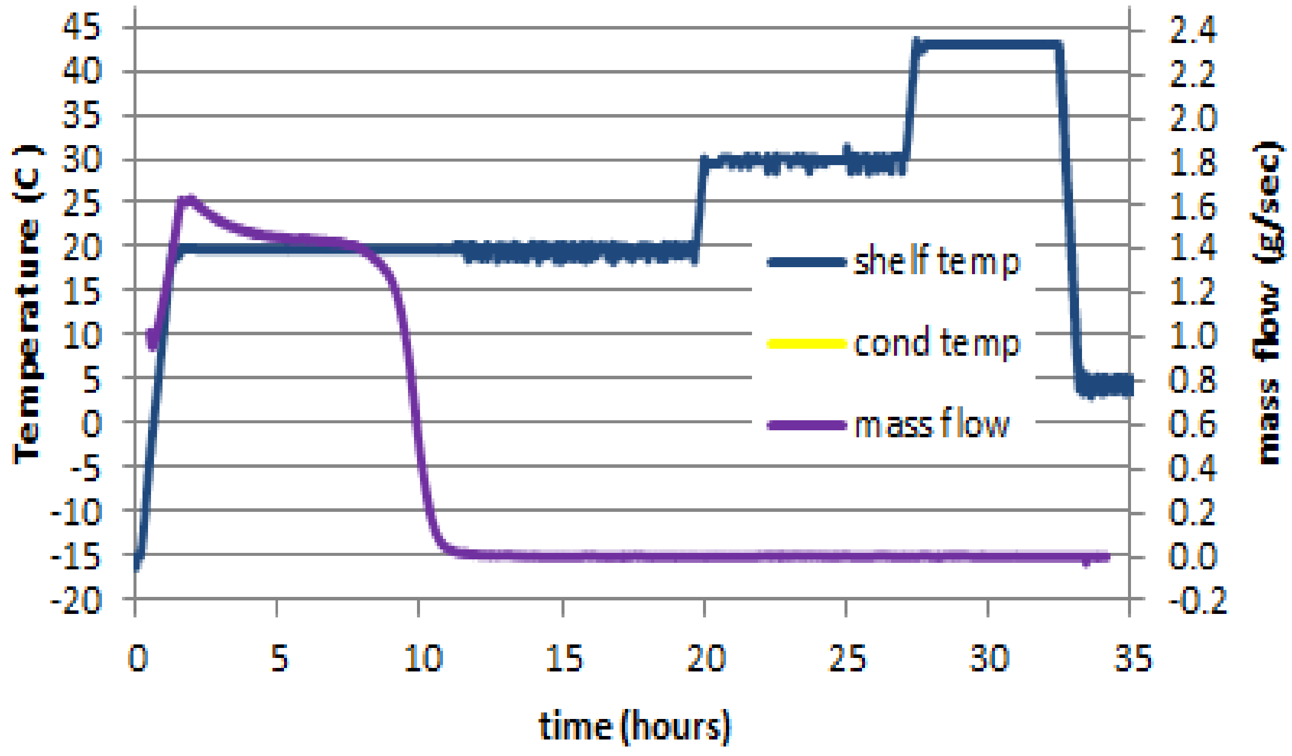






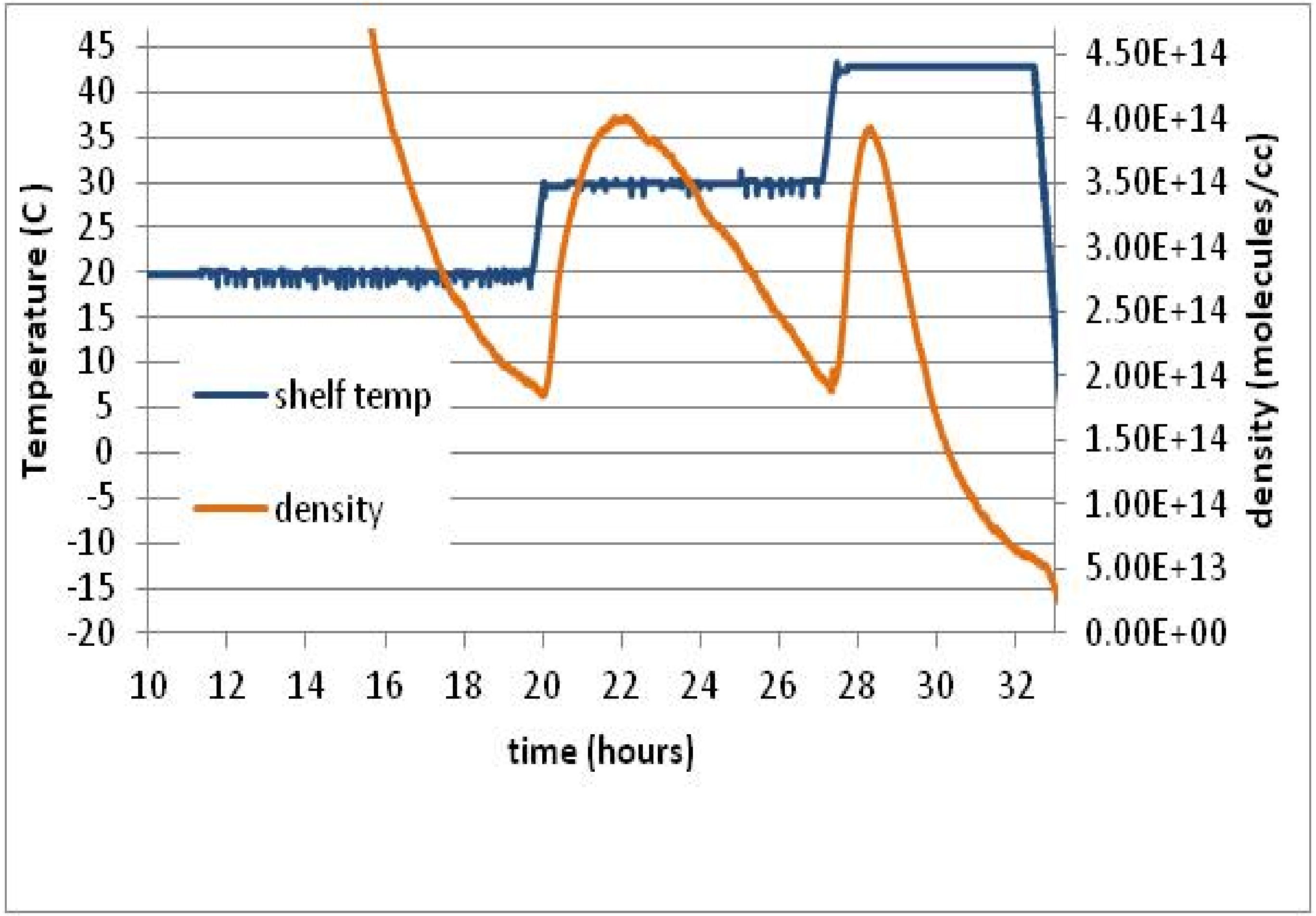


TDLAS Monitoring of Production Batches



Mass flow entire cycle BN 923428

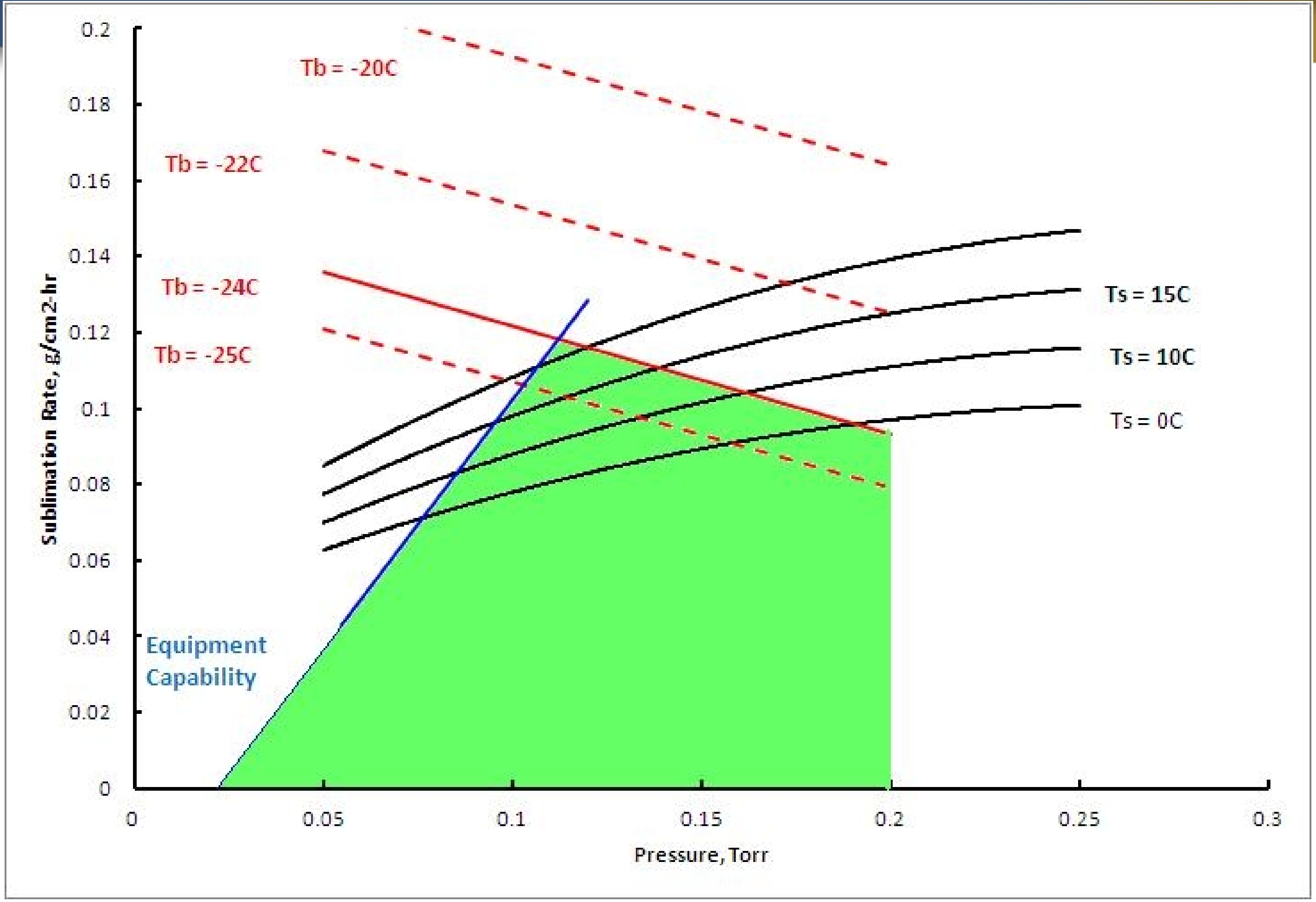
Example of Process Data: Water Vapor Density



Application of TDLAS in Pharm. Development

- Measurement of vial heat transfer coefficient
- Measurement of resistance of dry product layer to flow of wqter vapor
- Measurement of equipment capability
- Construction of a primary drying design space.

Example of a Primary Drying Design Space



PAT for On-Line Headspace Analysis

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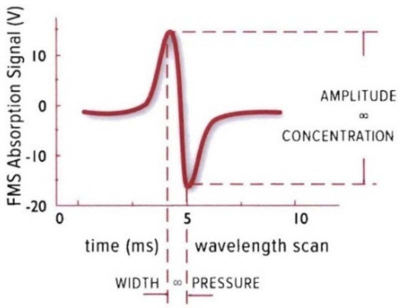
Frequency Modulation Spectroscopy

(tubing, molded, clear, amber)



- Modulation technique results in 10,000x increase in sensitivity compared to first order absorption techniques
- **Measurement time: ~ 1 sec**

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PAT for On-Line Headspace Analysis

PAT for On-Line Headspace Analysis

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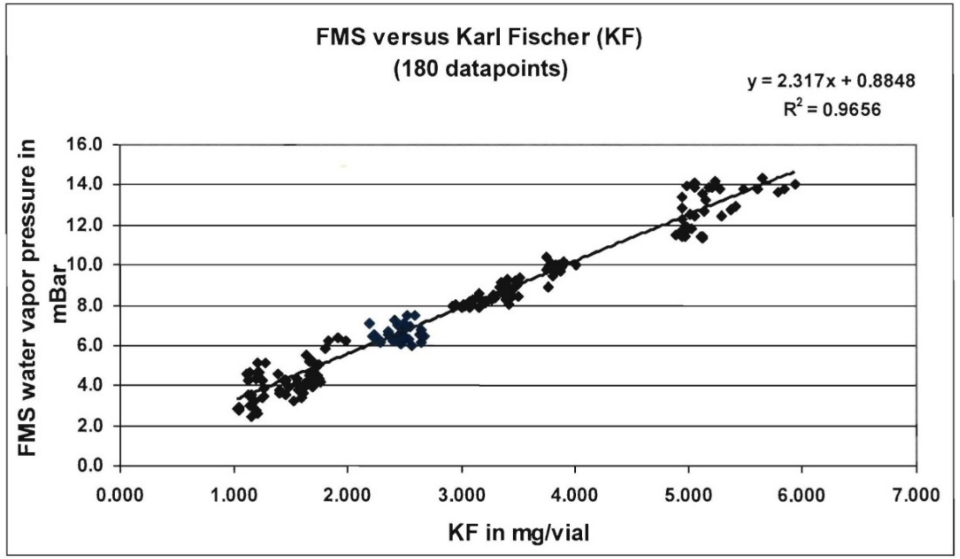
Correlation between Karl Fischer titration and Headspace Moisture



Lighthouse COMPANY CONFIDENTIAL

Ref: Data courtesy of Organon

Residual Moisture Mapping

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Moisture Mapping Case Study:

Freeze Dryer Characterization

Low value 0.4 torr = 1% KF
High value 3.2 torr = 4% KF

Colour key: 0.4-0.9 | 1.0-1.6 | 1.6-1.9 | 2.0-3.2

0.8	0.7	0.5	0.5	0.7	0.5	0.5	0.9	0.7	0.8	0.7	0.7	0.9	0.7	0.8	0.8	0.6	0.8	0.5	0.7	0.7	1.1	0.7
0.5	0.5	0.6	0.5	0.7	0.5	0.5	0.8	0.7	1.2	0.8	1.4	0.8	1.1	0.8	1.1	1.0	1.0	0.7	0.7	0.6	0.6	0.6
0.4	0.5	0.9	0.9	0.7	1.2	0.9	1.2	1.3	1.3		1.5	1.3	1.5	1.5	1.8	1.2	1.4	1.1	1.2	0.7	0.7	0.7
0.6	0.7	0.6	0.9	0.6	0.9	1.0	1.2	1.2	1.4	1.3	1.7	1.6		1.5	1.7	1.7	1.6	1.8	1.0	0.9	0.8	0.6
0.6	0.5	1.2	0.9	0.8	1.1	1.3	1.2	1.6	1.6	1.3	1.6						1.5	1.4	1.3	0.8	0.8	0.6
0.4	0.6	0.6	0.6	0.7	1.1	1.2		1.6	1.7	1.4	1.7			1.4				1.4	1.2	1.2	0.6	1.0
0.9	0.4	1.1	0.8	0.7	0.8	1.0	1.3	1.4	1.5		1.6		1.8		1.7		1.5	1.6	0.9	0.9	0.5	0.7
0.5	0.5	0.5	0.9	1.0	0.6	0.9	0.9	1.1	1.1		1.5	1.6	1.6	1.6	1.4	1.6	1.8	1.3	1.0	0.7	0.8	0.7
0.9	0.8	0.6	0.4	0.6	0.6	0.9	0.7	1.2	1.2	1.1	1.0	1.2	1.4	1.5	1.1	1.3	0.8	1.2	0.7	0.9	0.6	0.7
0.6	0.7	0.7	0.6	0.8	0.5	0.8	1.1	0.7	0.9	0.9	0.6	1.0	0.7	0.9	0.7	1.2	0.6	0.9	0.9	1.2	0.9	0.9
0.5		0.5		1.2		0.9		0.5		0.6		0.9		0.8		0.6		1.1		0.8		0.6

When using steel bottomed tray, headspace moisture plot shows high moisture samples in center of shelf

Data courtesy of Biopharma Technology Ltd
Cook et al.

PAT for On-Line Headspace Analysis

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Container closure integrity determination

Different types of defects can cause leakage in sterile vials:

Glass issues
- Cracks in glass
- Incoming glass defect
- Improper machine setup
- Rough handling

Seal issues
- Product on lip
- Improperly seated stopper
- Improperly applied cap
- Bad stopper / vial combination
- Stopper pop-up between lyo and capper

RESULT:
- **Increase O_2 levels**
- **Increase H_2O levels**
- **Decreased vacuum levels**

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PAT for On-Line Headspace Analysis

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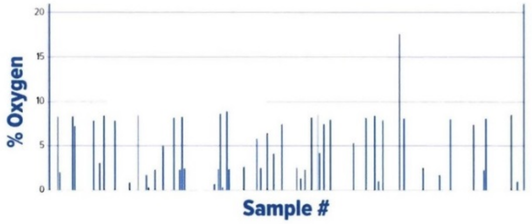
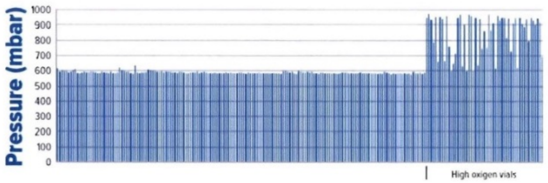
Industry case study

100% Container Closure Integrity Inspection

- Suspected raised stopper issue – batch of 11,000 lyo vials put into quarantine;
- 100% headspace inspection a few weeks after manufacture;
- Specified headspace conditions at stoppering was 600 mbar of nitrogen





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