

---

# **PAT for Freeze Drying: A Comparison of Methods for Primary Drying End Point Detection**

**Michael J. Pikal  
Sajal Patel  
School of Pharmacy  
University of Connecticut**

# Introduction

---

- Increasing the shelf temperature for secondary drying before all of the ice is removed from the product will likely **cause collapse or eutectic melt and loss of product quality.**
- Freeze-drying is an expensive process with relatively long processing time.
- Key objective is to decrease the cycle time as much as possible without causing product collapse

# Techniques to Determine End Point of Primary Drying

---

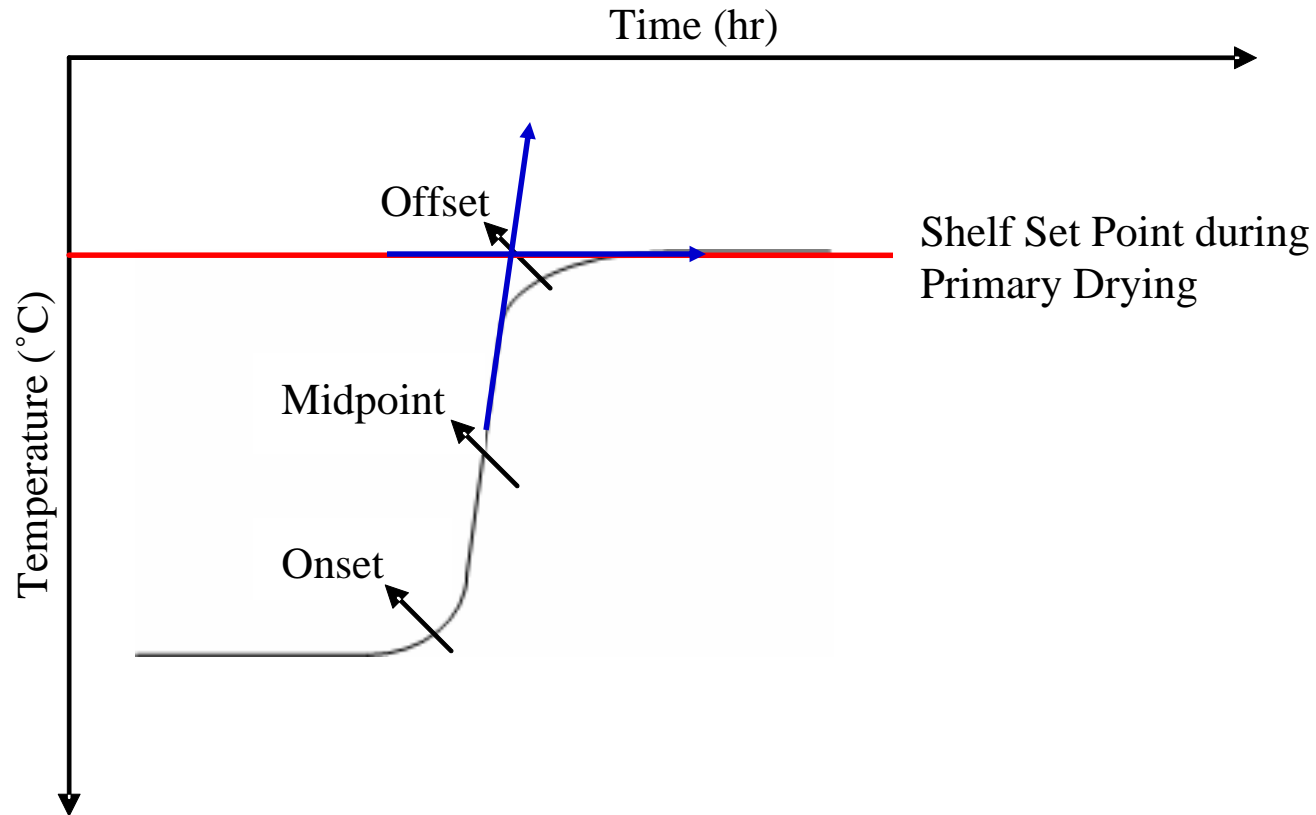
**Based on Gas Composition: H<sub>2</sub>O in 1° drying, N<sub>2</sub> in 2° drying**

- Comparative pressure measurement (i.e., Pirani vs. Capacitance Manometer)
- Dew point (electronic moisture sensor)
- H<sub>2</sub>O concentration from TDLAS (Tunable Diode Laser Absorption Spectroscopy)
- Lyotrack: Gas plasma spectroscopy

**Others:**

- Product thermocouple response
- Pressure rise test (Manometric Temperature Measurement (MTM))
- Condenser Pressure

# Product Thermocouple (TC) Response



# Problems with Product TC Response

---

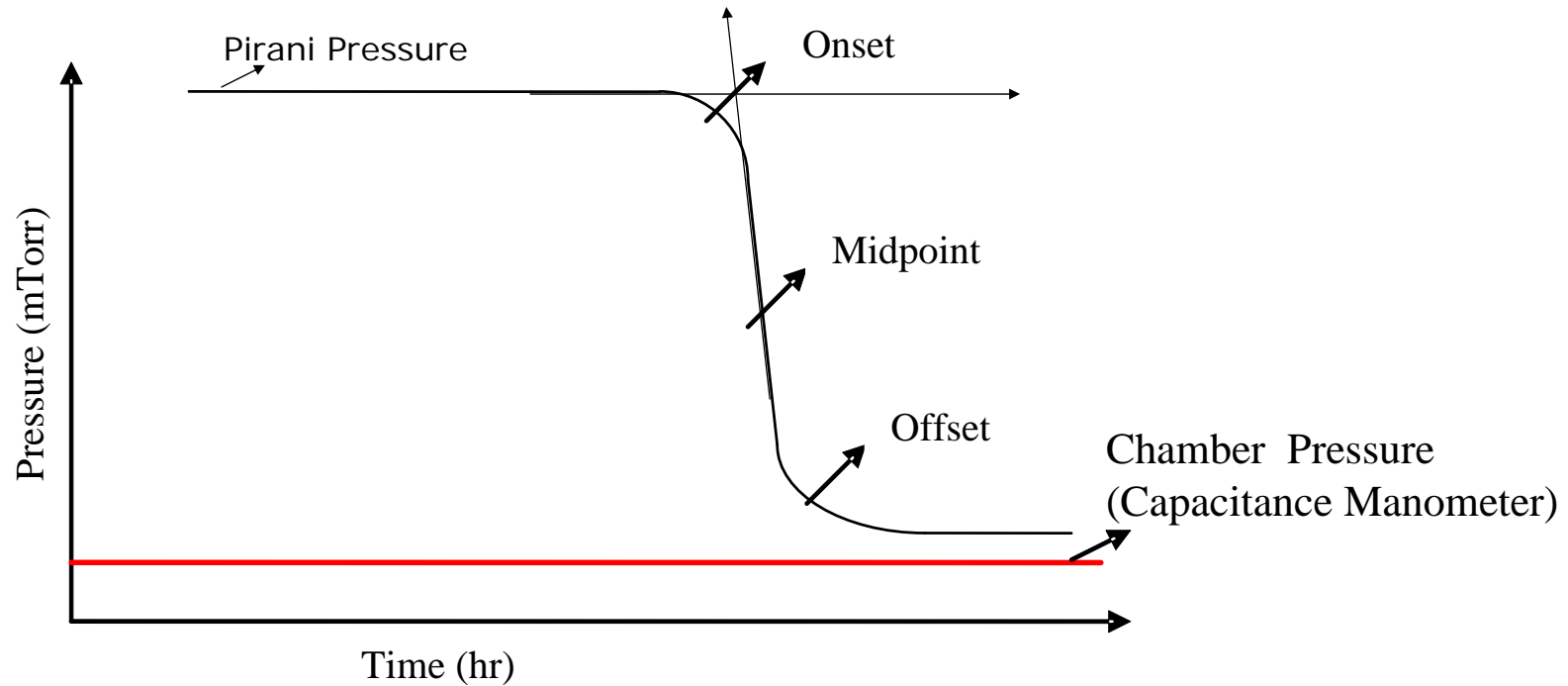
- Not representative of the entire batch
  - ➔ Vials containing TC freeze-dry differently than vials without TC
- With automatic loading system difficult to place TC
- Edge vial effect
- Invasive technique

# Comparative Pressure Measurement

---

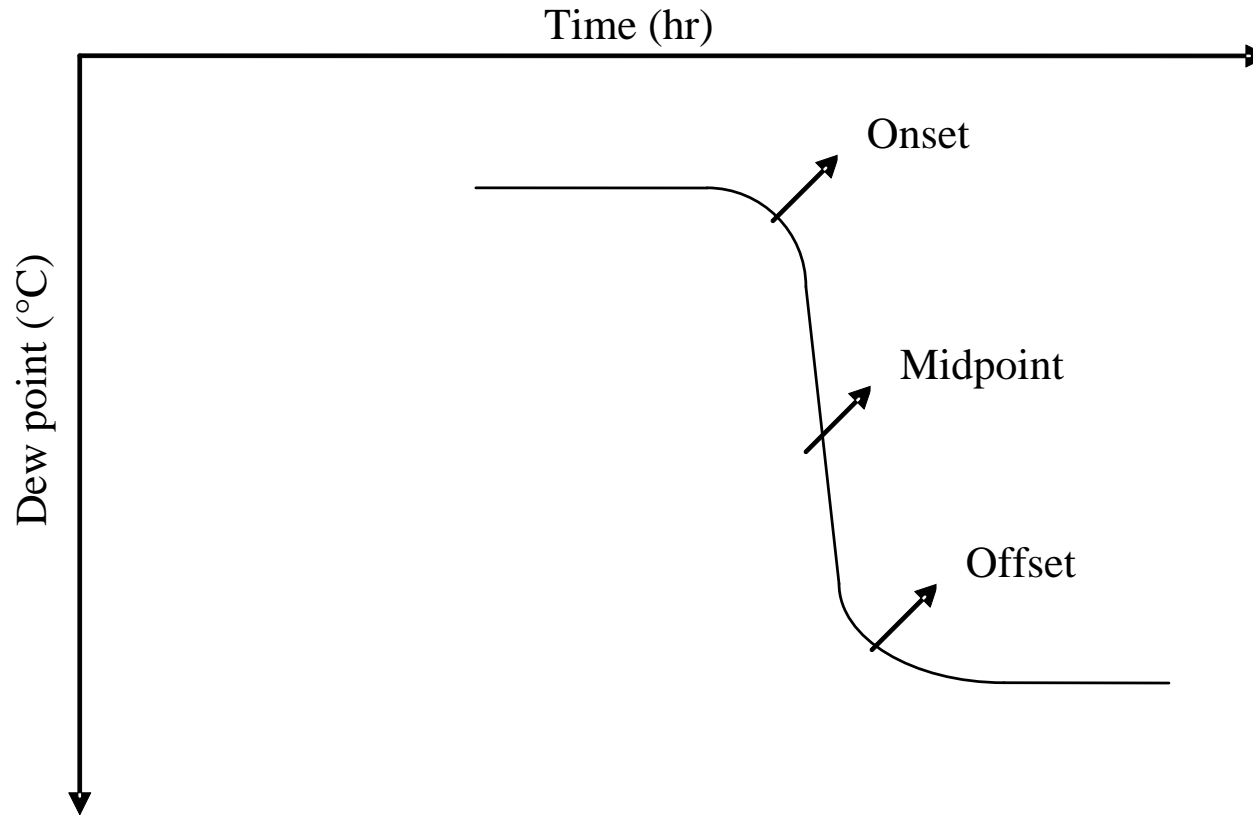
- Capacitance Manometer
- Pirani Gauge

# Comparative Pressure Measurement

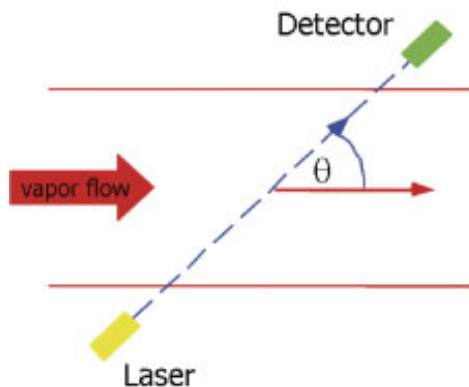
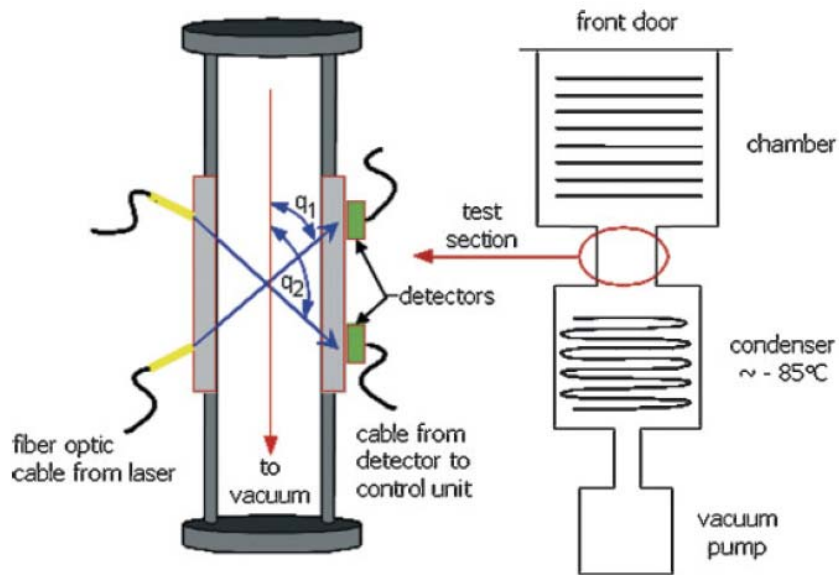


# Dew Point (Electronic Moisture Sensor)

---

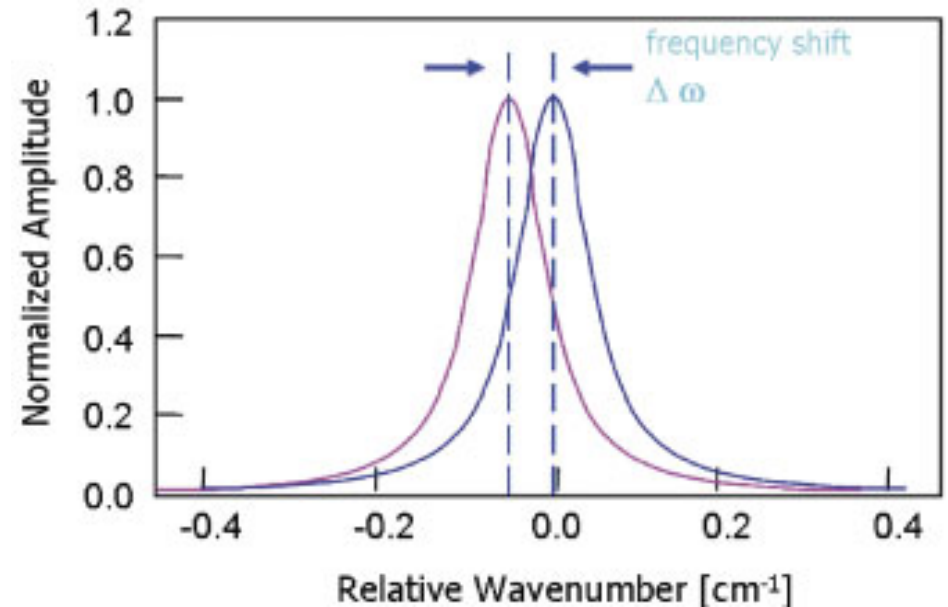


# Tunable Diode Laser Absorption Spectroscopy



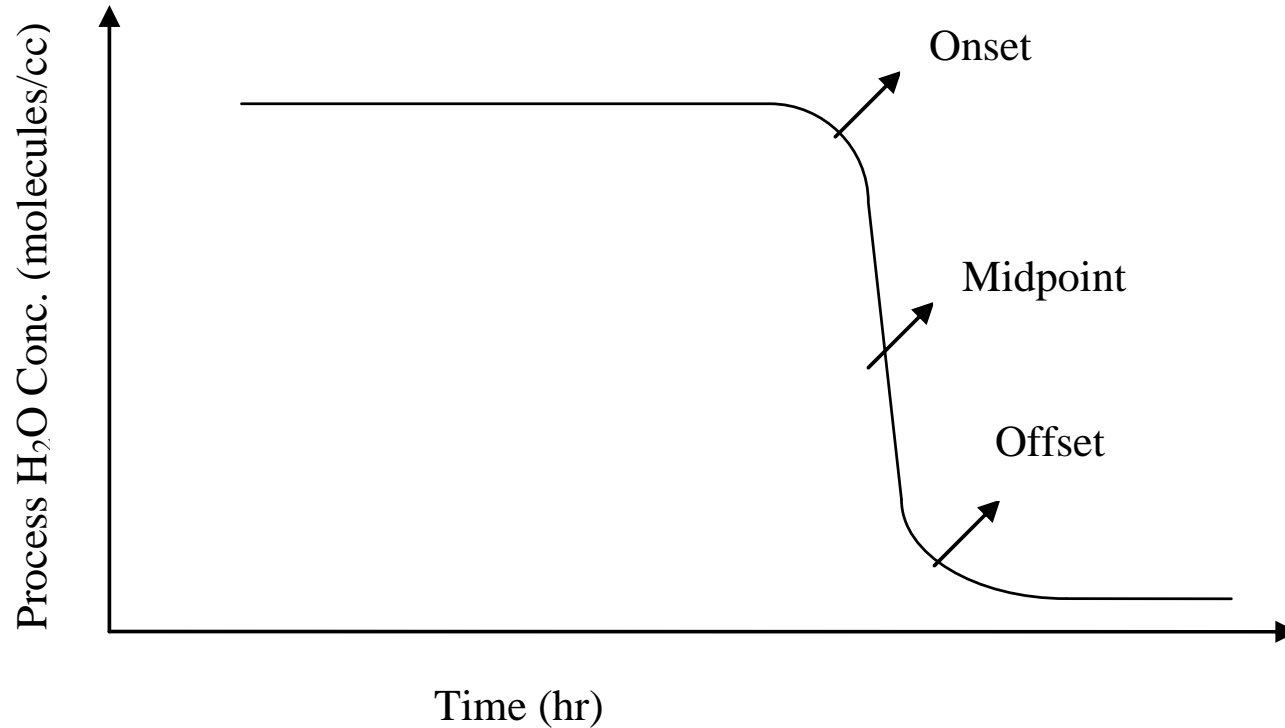
$$\frac{dm}{dt} = N \cdot u \cdot A \quad u = \frac{c \cdot \Delta\omega}{\omega_0 \cdot \cos \theta}$$

## Doppler Shift



# Process H<sub>2</sub>O Concentration from TDLAS

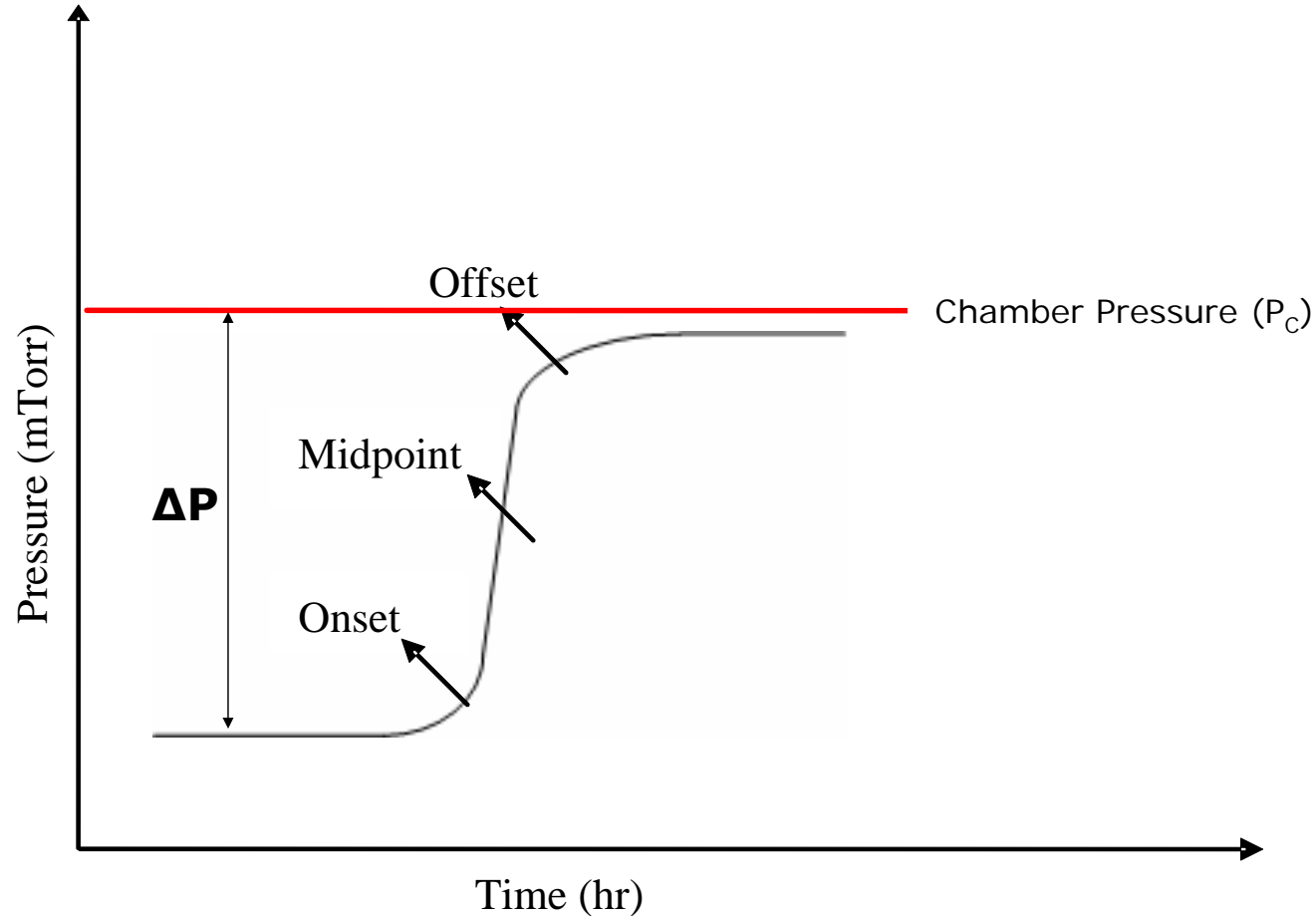
---



# Condensate Pressure

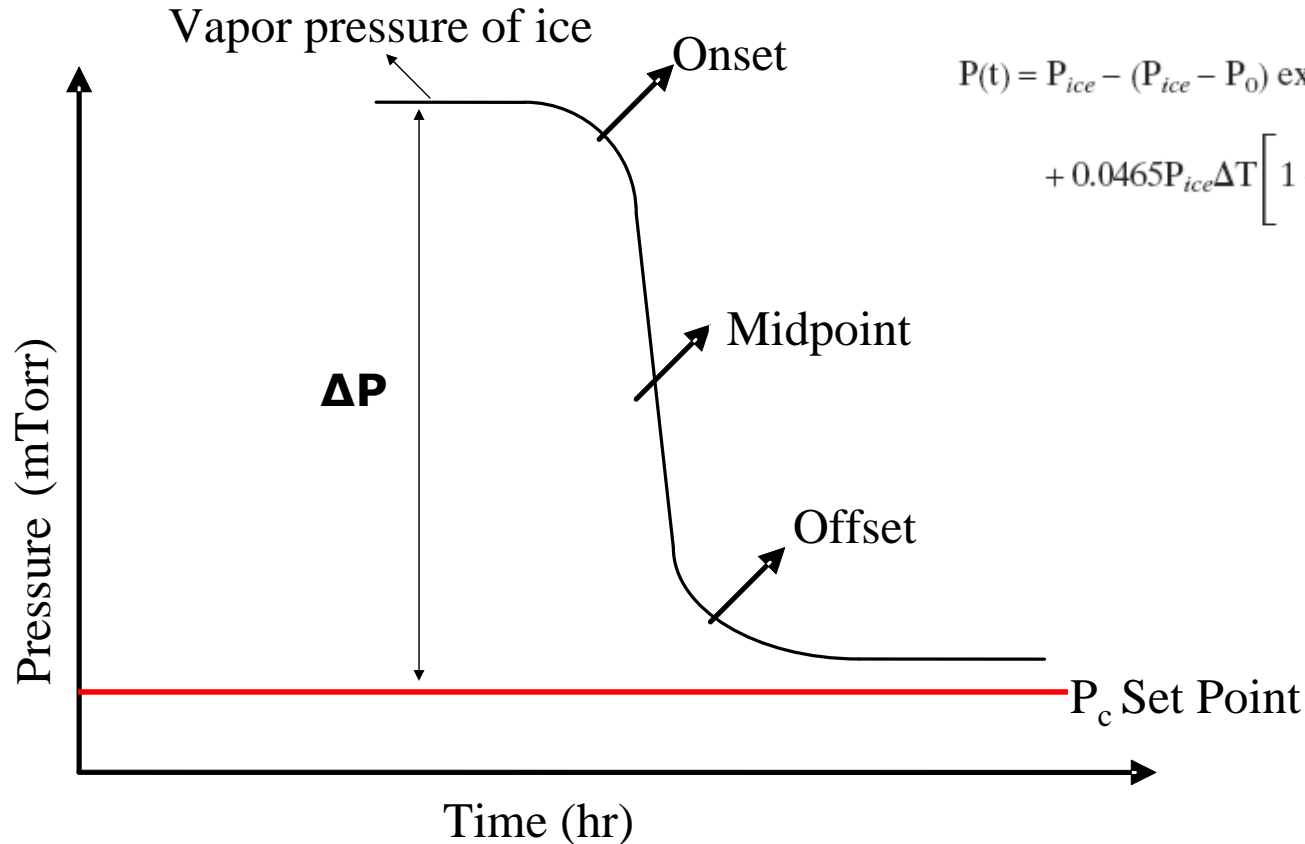
Large  $\Delta P$  to support large mass flux in 1° drying

---



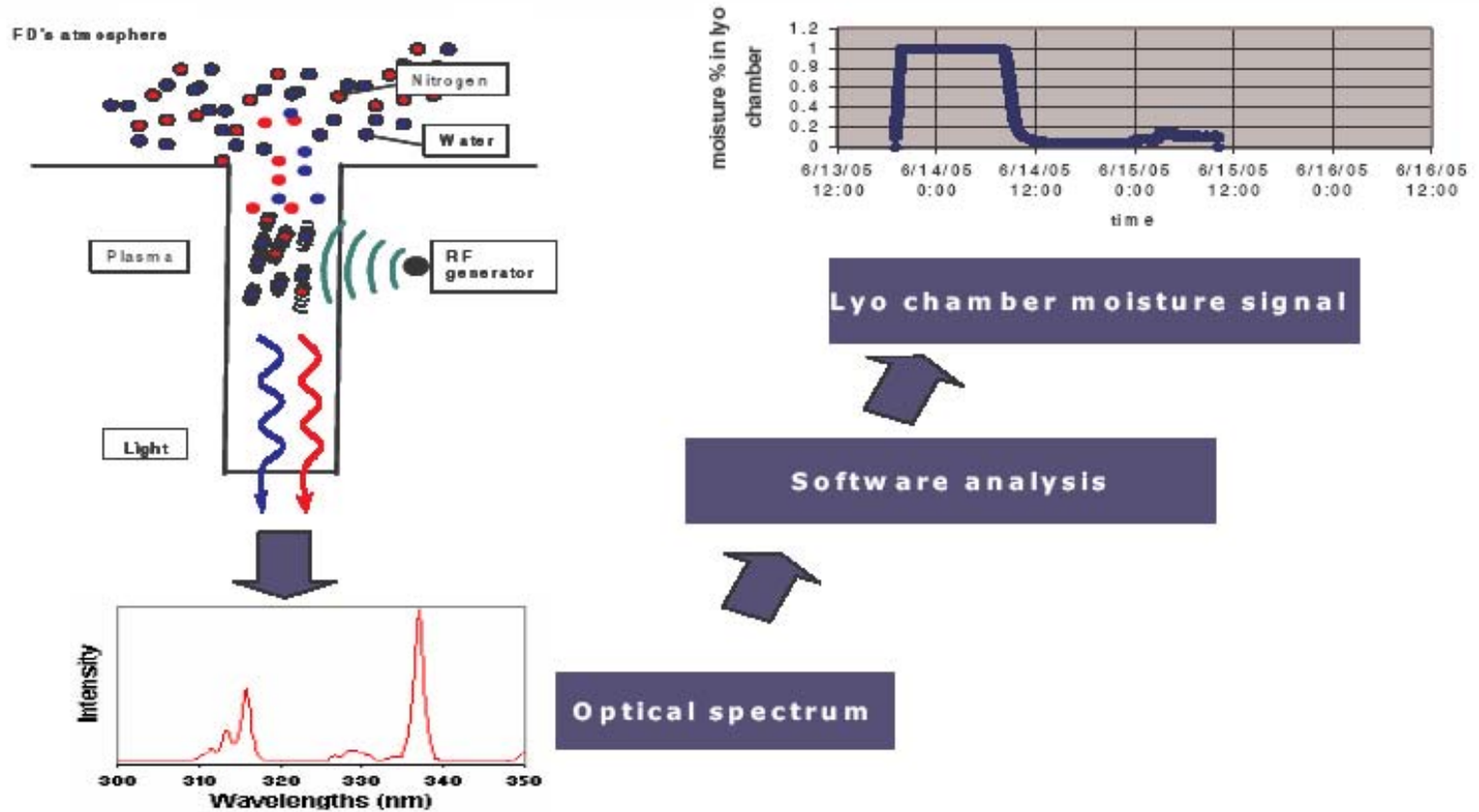
# Pressure Rise Test/MTM

## $\Delta P$ LARGE in Primary Drying



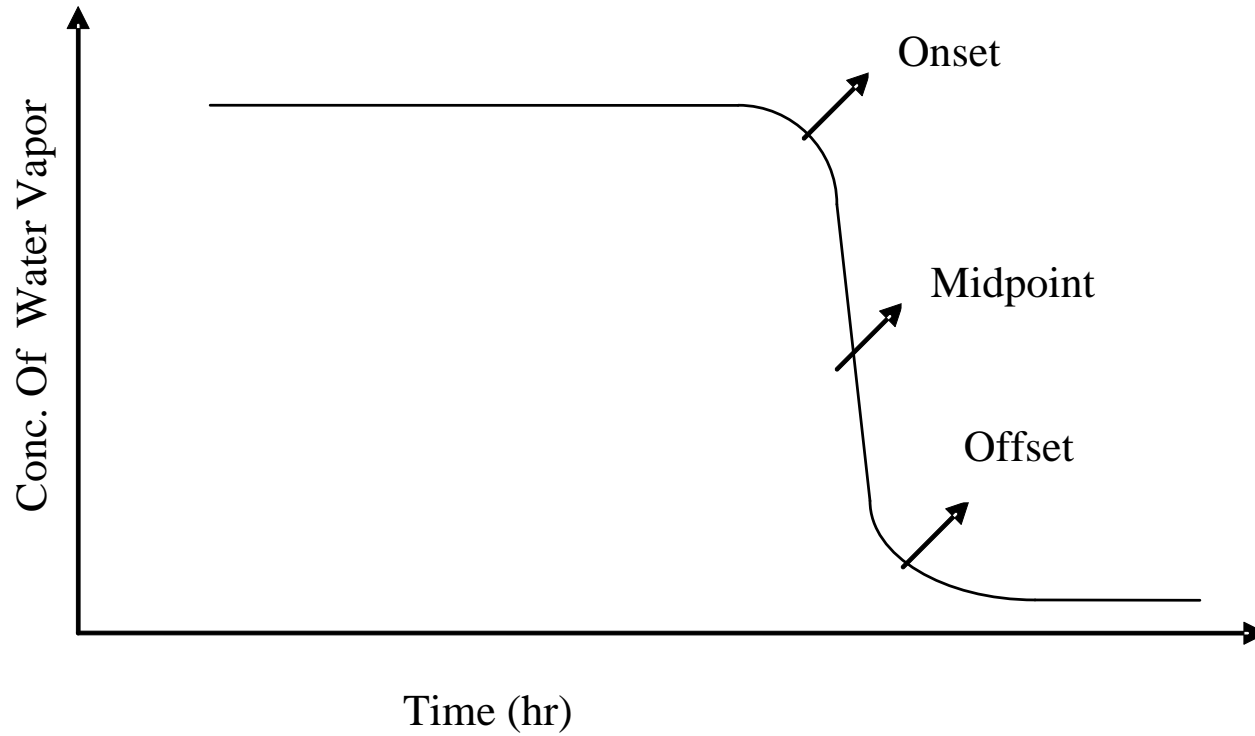
$$P(t) = P_{ice} - (P_{ice} - P_0) \exp\left[-\left(\frac{3.461NApT_s}{V(\hat{R}_p + \hat{R}_s)}\right)t\right] + 0.0465P_{ice}\Delta T\left[1 - 0.811 \exp\left(-\frac{0.114}{L_{ice}}t\right)\right] + X_t$$

# LyoTrack – Humidity Monitoring Tool



# Lyotrack

---



# Critical Questions

---

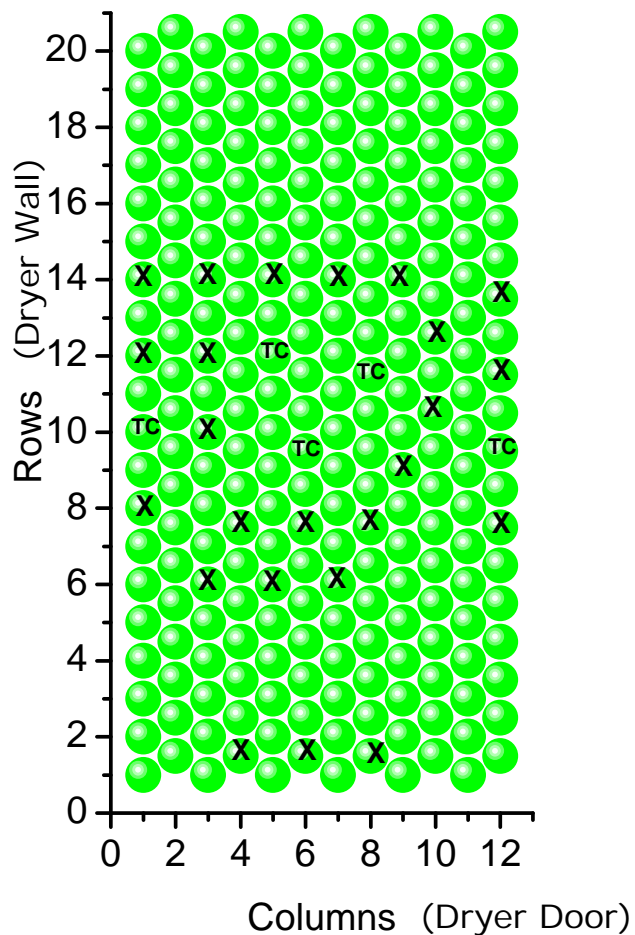
- What is the water content at the end of primary drying as determined by the various techniques?
- Has all ice been removed, and is the water content sufficiently low to avoid collapse if the temperature is increased for secondary drying?

# Material and Methods

---

- 5% (w/v) Mannitol and 5% (w/v) Sucrose
- 10cc, 20mm vials with 3mL fill volume
- Freezer-dryer: Lyostar II (SP Industries, NY)
- Samples were extracted from the chamber using the sampling thief assembly

# Vial Array



X = Sampled vials,

TC = Vials containing thermocouple

# Analysis of Product

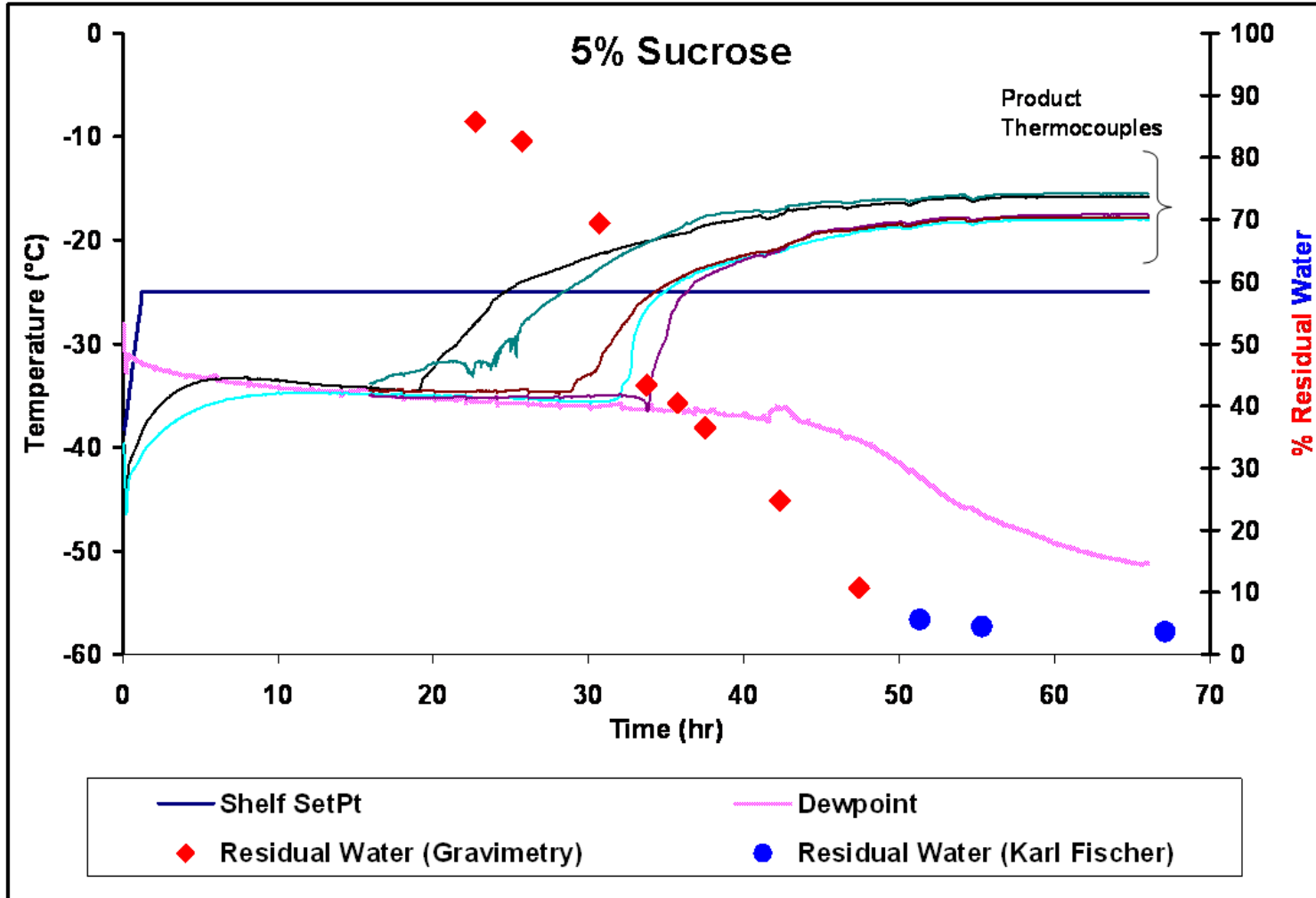
---

- **Residual Water Determination:**
  - Gravimetric: When the vials selected had a complete melt back (i.e, “puddle of solution”) after warming to room temperature, due to presence of ice
  - Karl Fischer: For the vials that retained cake structure
- **Visual characterization:**
  - A) Melt back
  - B) Cake collapse,
  - C) Cake structure.

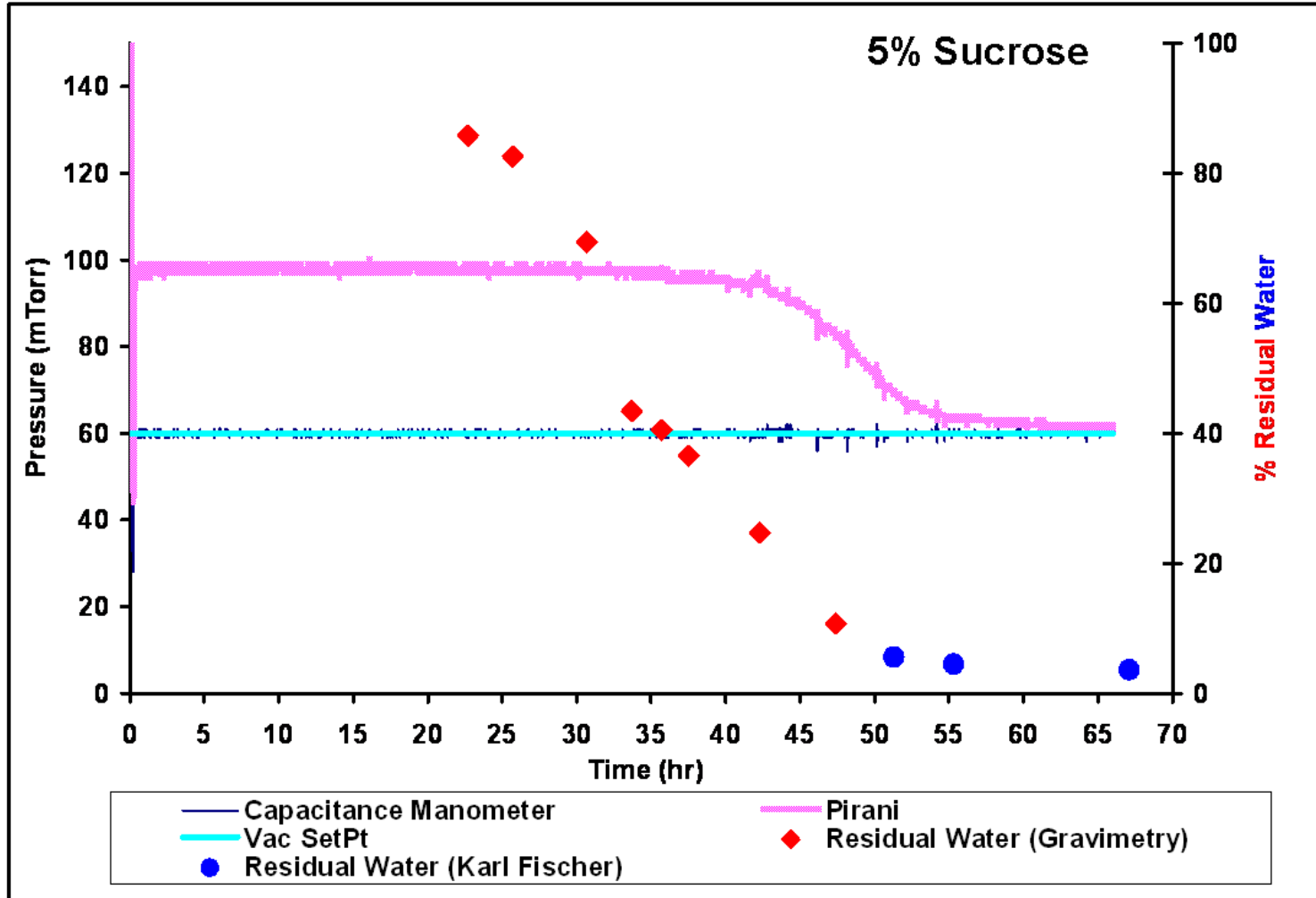
---

# Results

# Product TC and Dew Point

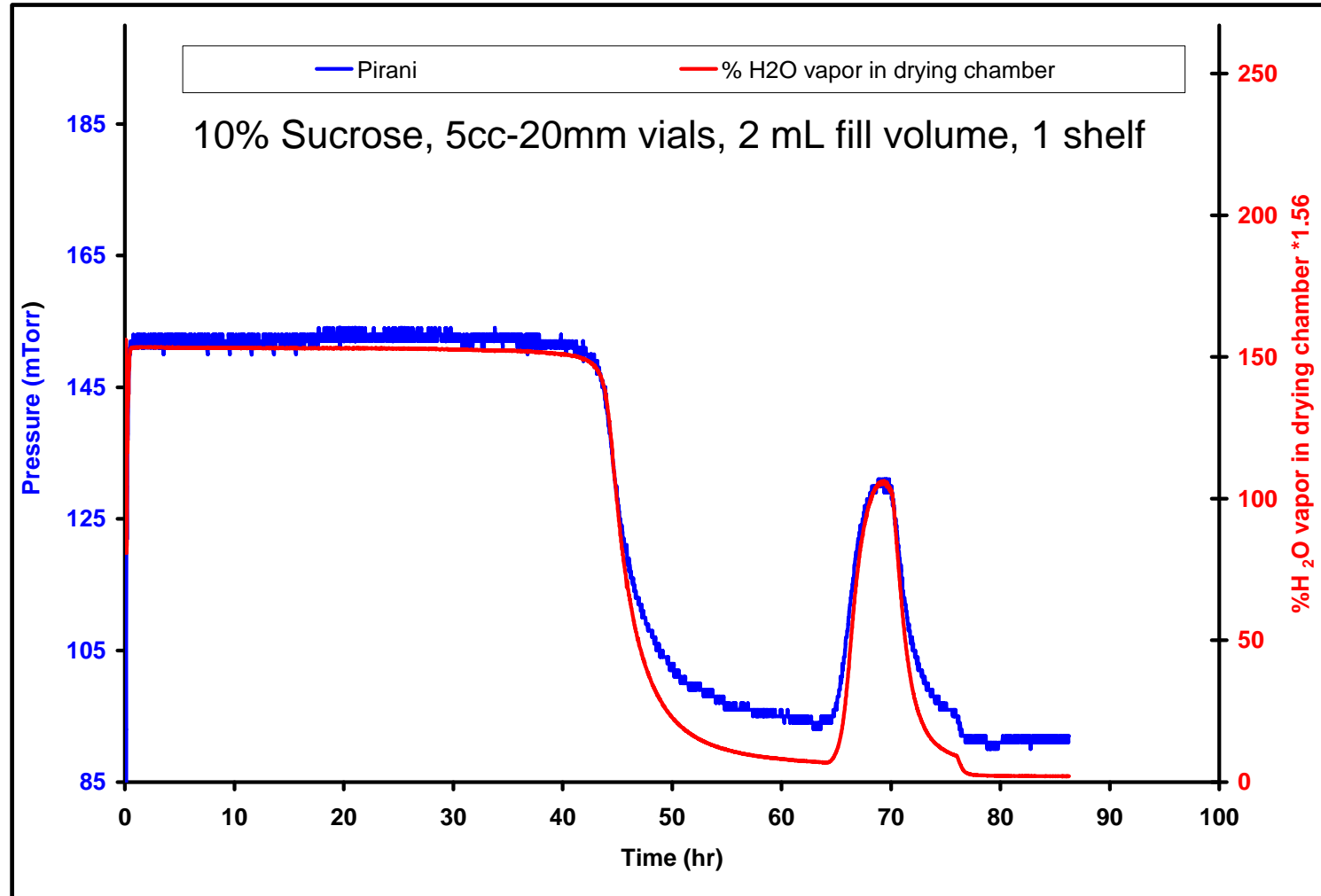


# Pirani Pressure



# Pirani vs. Lyotrack

## Essentially the Same Response

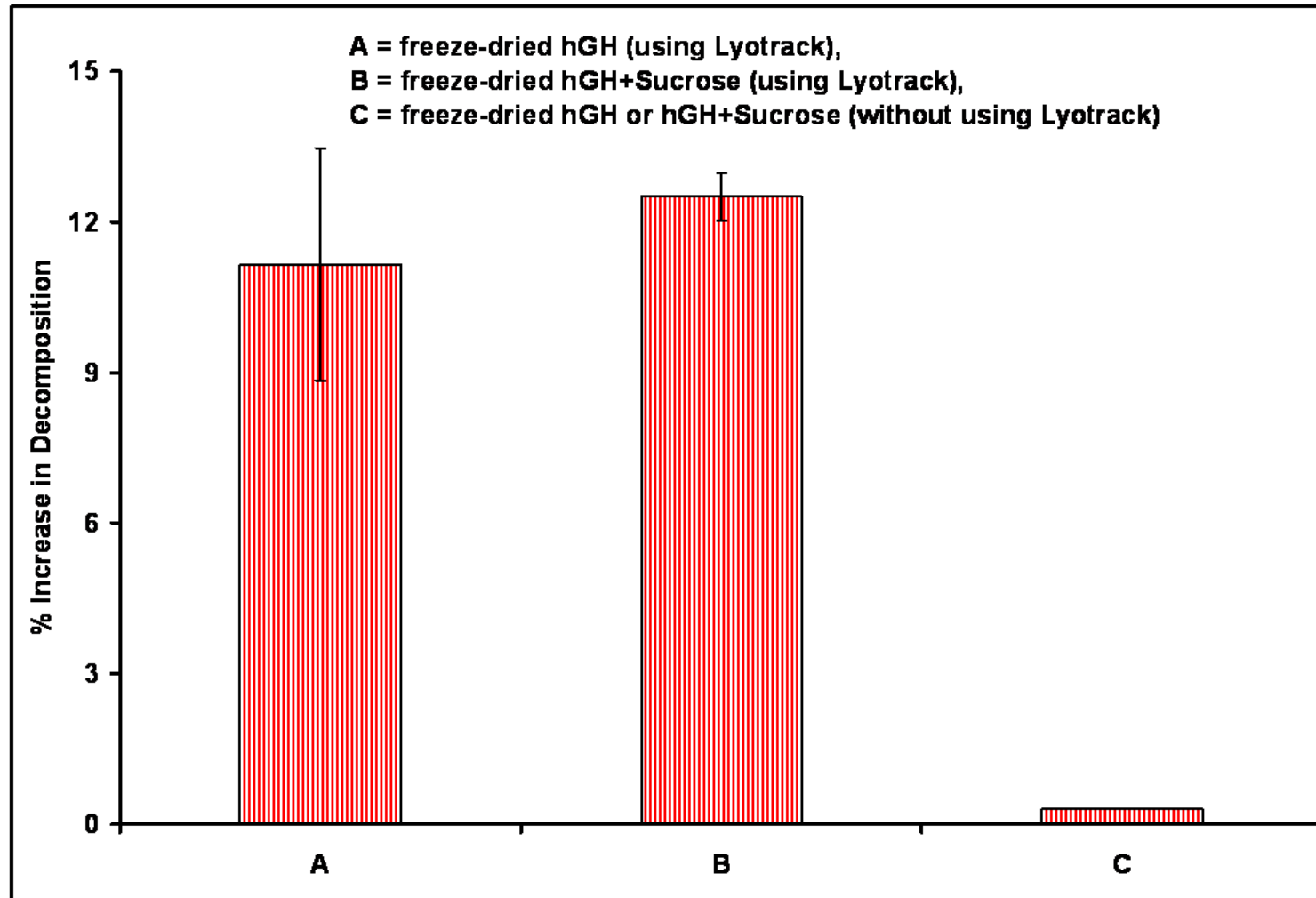


# Lyotrack – Free Radical Oxidation Issue

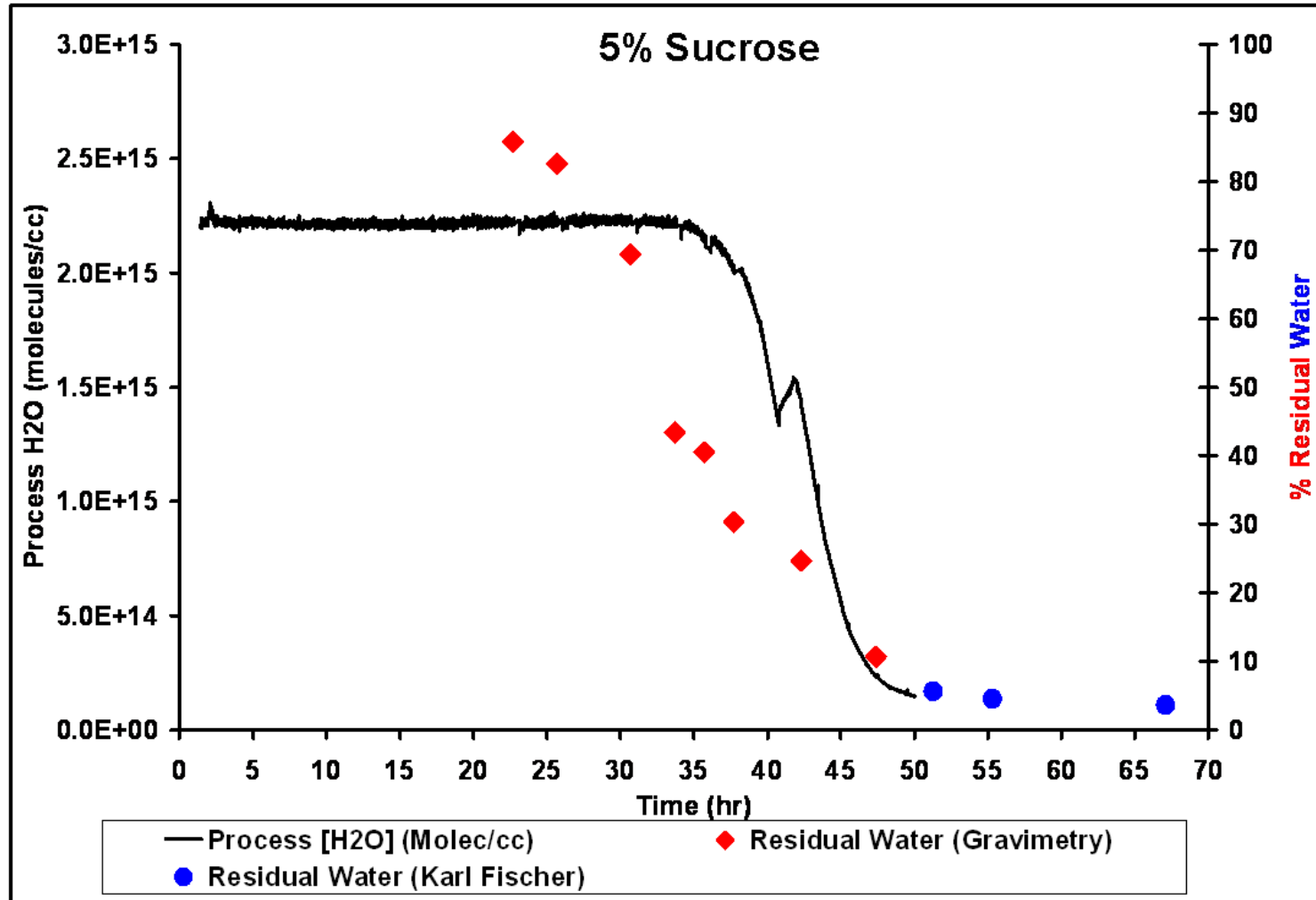
---

- Ionizes the gas present in the chamber
- Plasma: Partially ionized gas containing atoms, molecules and ions with free electrons (i.e., free radicals)
- **Free radical oxidation**

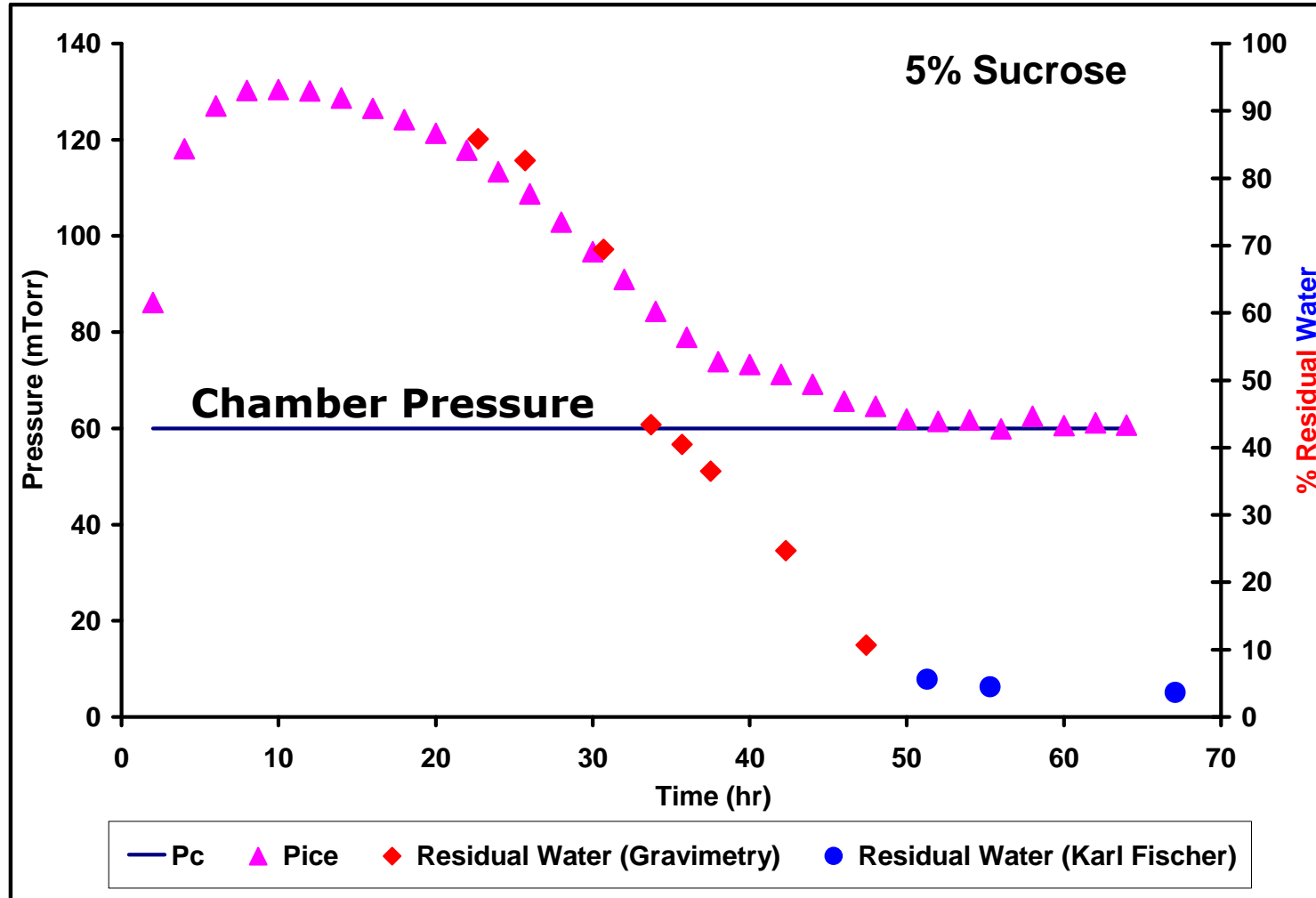
# Lyotrack – Potential Oxidation Issue



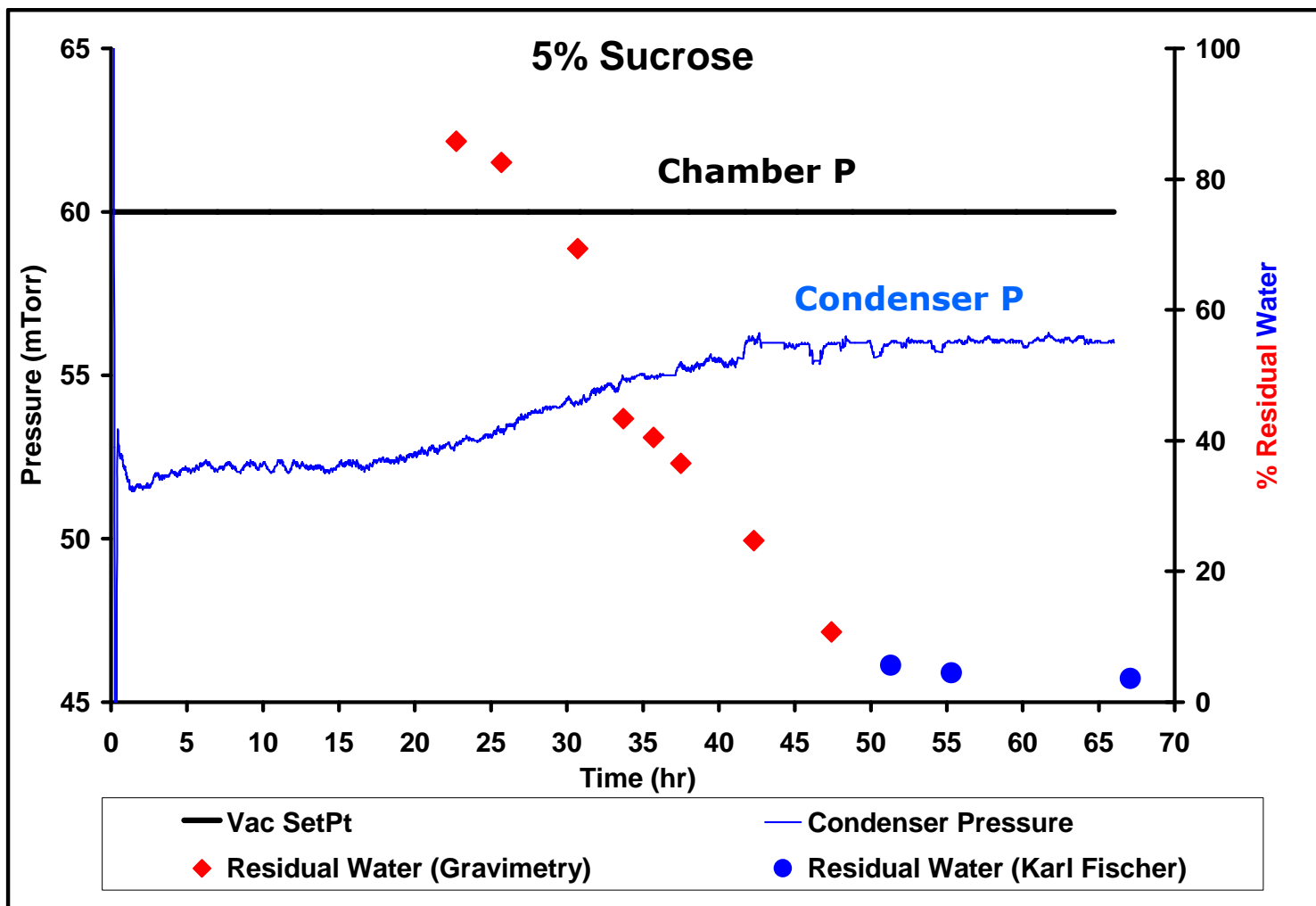
# H<sub>2</sub>O Concentration from TDLAS



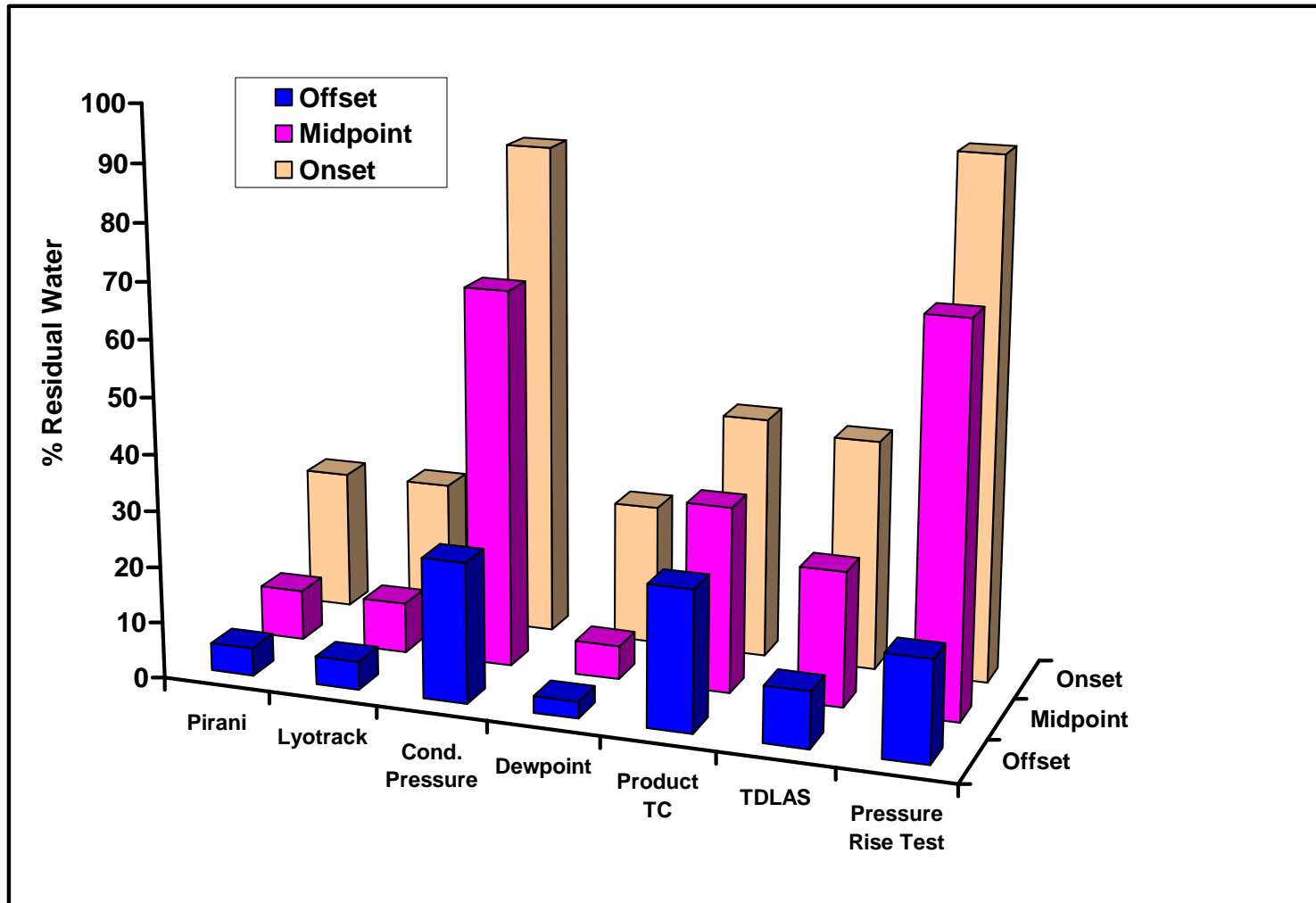
# Pressure Rise Test/MTM



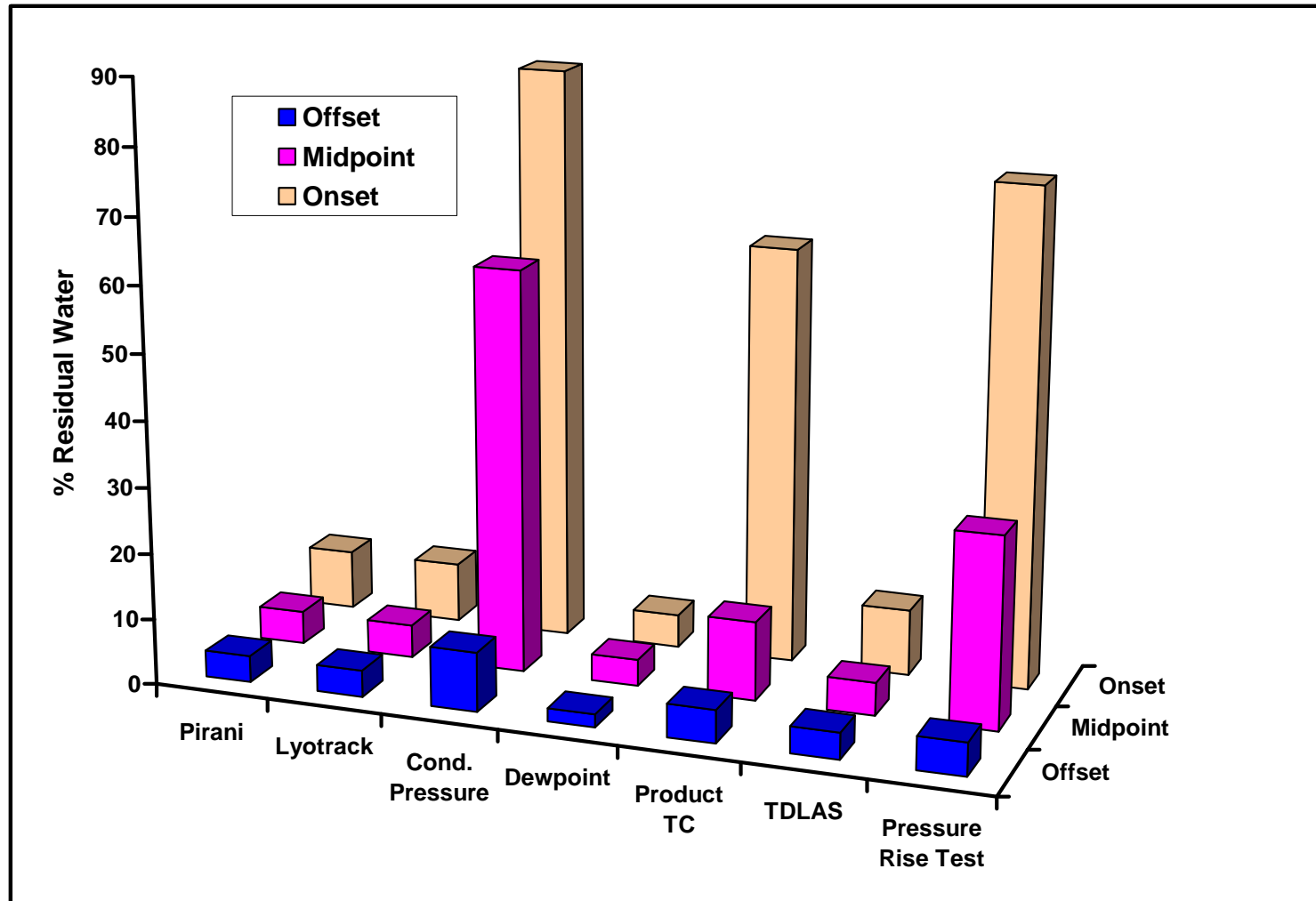
# Condenser Pressure



# Residual Water (5% Sucrose)






# Residual Water (5% Mannitol)



# Cake Appearance/ % Residual Water

Indicator (5% Sucrose)	%Residual Water		
	Onset	Midpoint	Offset
Pirani	24	9	5
Lyotrack	24	9	5
Condenser Pressure	88	67	25
Dewpoint	24	6	3
Product TC	43	33	25
TDLAS	41	24	10
Pressure Rise Test	92	69	18

Indicator (5% Mannitol)	%Residual Water		
	Onset	Midpoint	Offset
Pirani	9	5	4
Lyotrack	9	5	4
Condenser Pressure	87	61	9
Dewpoint	5	4	2
Product TC	63	12	5
TDLAS	10	5	4
Pressure Rise Test	75	29	5

Cake Appearance:  = Melt Back  = Collapse  = Cake

**bad**                      **OK**                      **Good**

# Summary

Factors	Product TC	DP	TDLAS	Cond. Pressure	PRT or MTM	Lyotrack	Comparative Pressure Measurement
Monitor Entire Batch	Red	Green	Green	Green	Green	Green	Green
Auto Loading	Red	Green	Green	Green	Green	Green	Green
C.I.P + Stoppering device	Red	Green	Green	Green	Green	Green	Green
Aseptic handling	Red	Green	Green	Green	Green	Green	Green
Steam Sterilization	Green	Red	Green	Green	Green	Green	Green
Leak rate insensitive	Green	Green	Green	Red	Red	Green	Green
Implementation	Green	Green	Red	Green	Green	Green	Green
Calibration	Green	Green	Green	Green	Red	Red	Green
Cost \$\$\$	Green	Green	Red	Green	Green	Red	Green
Robust	Yellow	Yellow	Green	Yellow	Green	Green	Green

Red = No

Green = Yes

Yellow = Maybe

# Conclusions

---

- Pirani is, by far, the best method for the detection of end point of primary drying
- TDLAS and MTM gives other useful information apart from monitoring end point of primary drying