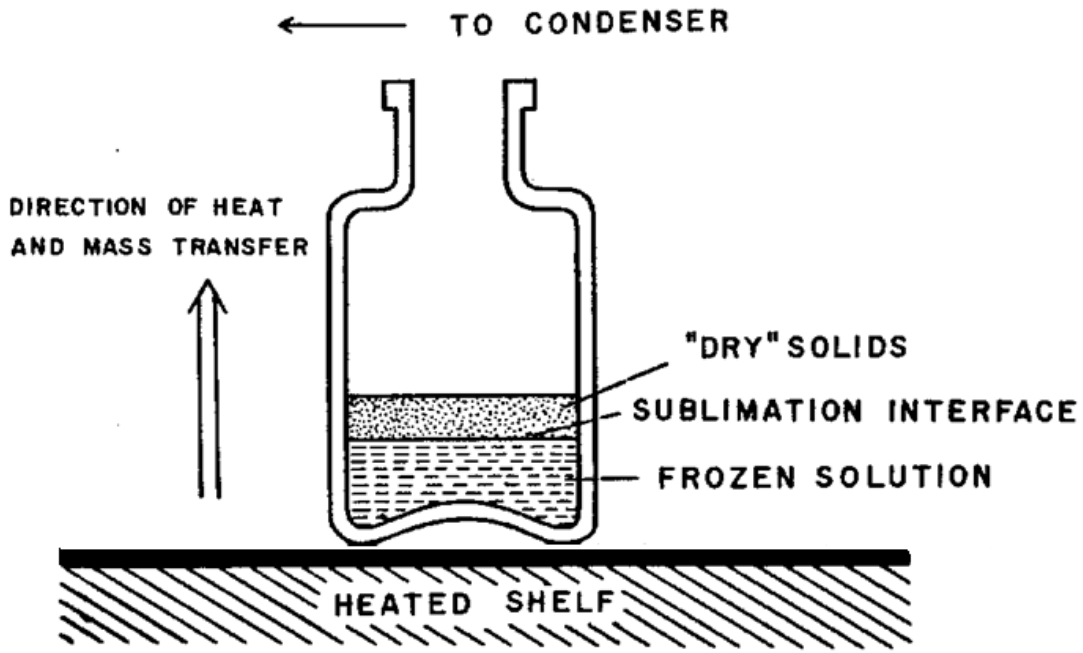
Fundamentals of Freeze Drying

Lyo-Hub Summer School

Part 3 – Primary and Secondary Drying

Cycle Development: Why Do We Pay Particular Attention to Primary Drying

- **It usually takes longer than any other part of the cycle.**
- **It presents the greatest risk to product quality.**



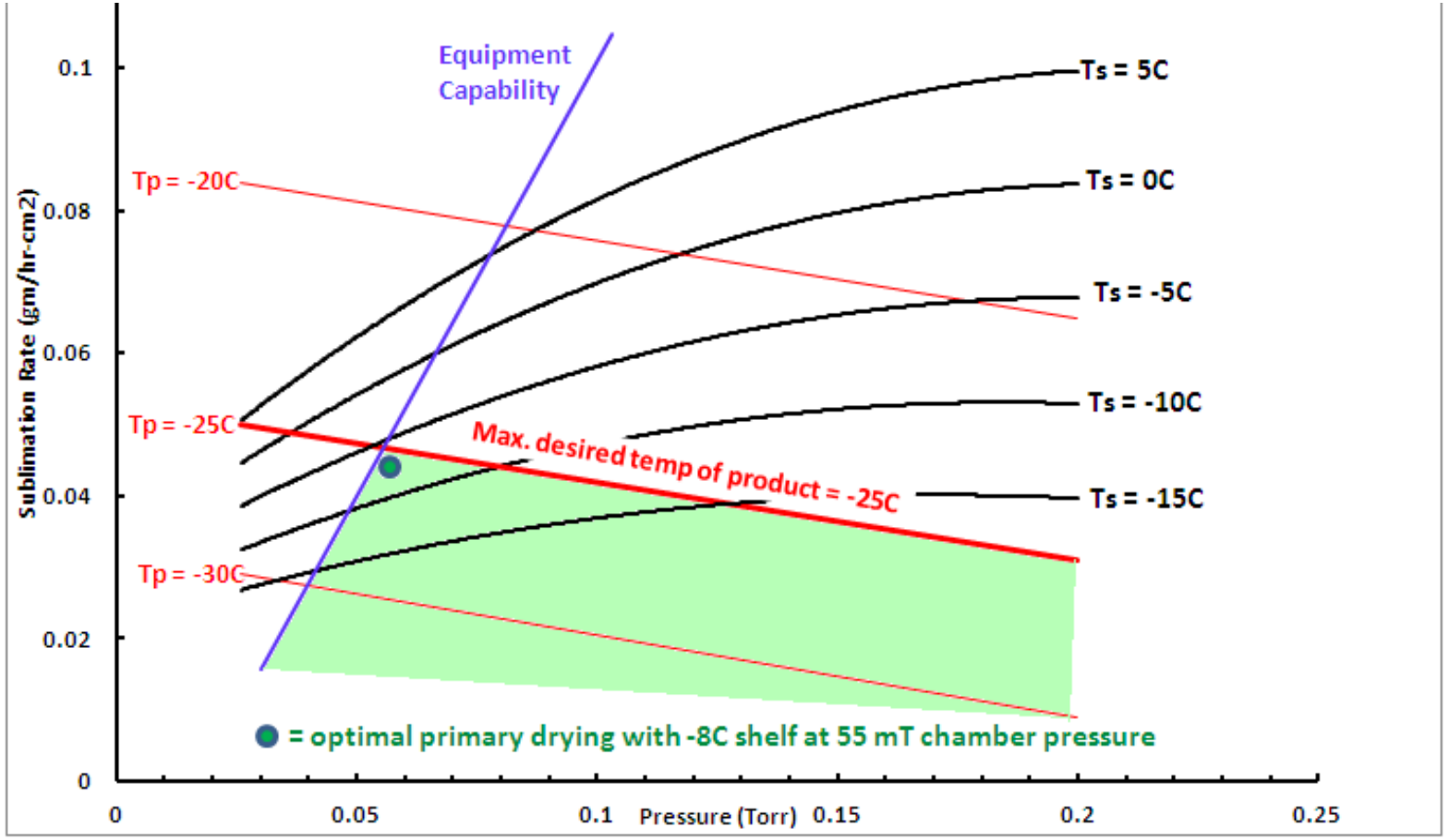
“Traditional” Approach to Freeze-Dry Cycle Development

- **Largely by trial and error, identify freeze-dry process conditions that produce an acceptable product.**
- **Establish “proven acceptable ranges” around shelf temperature and chamber pressure set points.**

QbD Approach to Cycle Development

- **Identify optimal processing conditions based on a thorough understanding of the process, and *find the edges of failure.***

Graphical Design Space



Outline of Steps

- **Characterize the formulation and identify the failure mode**
  - **Eutectic melting (“melt-back”)**
  - **Collapse**
  - **Powder ejection from the vial?**
  - **Others?**
- **Determine the upper product temperature limit during primary drying**
  - **Freeze dry microscopy**
  - **Trial laboratory batches where we try to “make it fail,” looking for failure based on visual observation of the freeze-dried product.**

Outline of Steps

- **Establish the relationship between the process variables you control (shelf temperature and chamber pressure) and the one you don't directly control (product temperature).**
  - **Measure the vial heat transfer coefficient, K_v, as a function of chamber pressure**
  - **Measure the resistance of the dried product layer, R_p, to flow of water vapor**

Mechanisms of Heat Transfer

- **Conduction**
- **Convection?**
- **Thermal radiation**

Equations for Heat and Mass Transfer

$$dq/dt = K_v A_v (T_s - T_b)$$

$$dm/dt = A_p (P_i - P_c)/R_p$$

$$dq/dt = \Delta H_s \, dm/dt$$

Assumptions

- This approach assumes a constant shelf temperature, T_s, during primary drying.
- It also assumes a constant value of R_p, the resistance of the dried product layer. We know that the resistance should increase throughout primary drying, as the thickness of the partially dried layer increases. The value of R_p that we use is the value at the end of primary drying, where product temperature, and risk to the product, is highest.
- In establishing the equipment capability curve for the laboratory/pilot dryer, we assume a full freeze dryer, even though this is seldom done.

Measurement of K_v

- **Fill the intended vial with the intended volume of water. Note: We use one full tray in the Lyo-Star**
- **Place thermocouples in the bottom center of several vials – minimum of three**
- **Carry out the freeze dry cycle at an appropriate shelf temperature and at the low end of the intended pressure range**
- **Monitor mass flow rate by TDLAS or "Smart Freeze Dryer" software until it stabilizes, then change to a new pressure set point. Keep repeating until youve covered the selected pressure range.**
- **Calculate K_v at each pressure using the relationship:**

$$K_v = \Delta H_s \, dm/dt/[A_v(T_s - T_b)]$$

Example:

Pressure (mT)	K_v (j/hr-cm^2-^{o}K)
25	3.58
50	5.25
75	6.11
100	7.24
125	8.20
150	9.01
175	9.75
200	10.31
250	11.21
300	12.07
350	12.92
400	13.77

Measurement of R_p

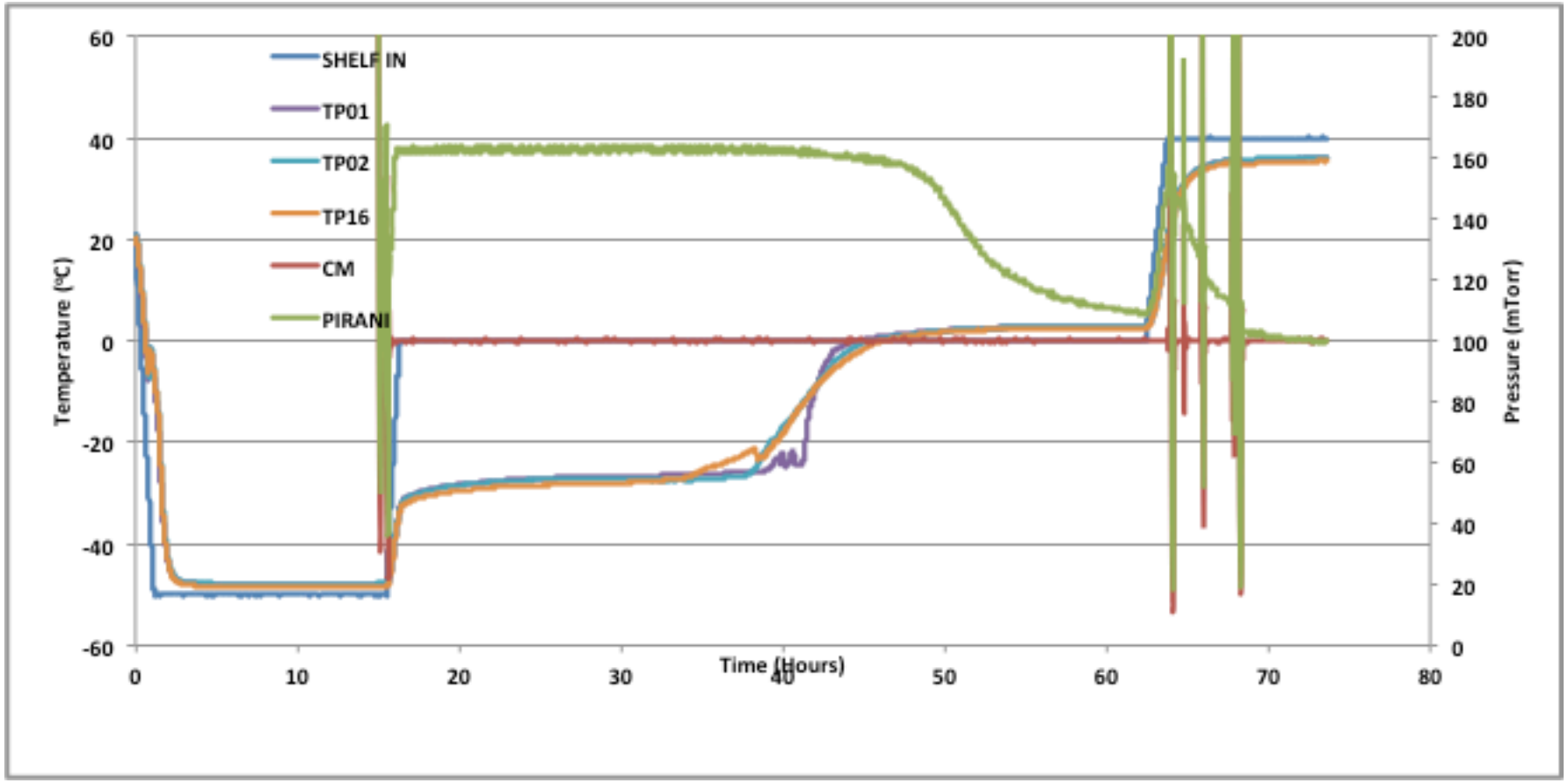
- Fill the intended vial with the correct volume of formulation in the intended vial and run a trial cycle.
- Place thermocouples in at least three vials.
- Monitor mass flow rate by TDLAS or “Smart Freeze Dryer”.
- Calculate R_p as follows:

$$R_p = A_p(P_i - P_c)/(dm/dt)$$

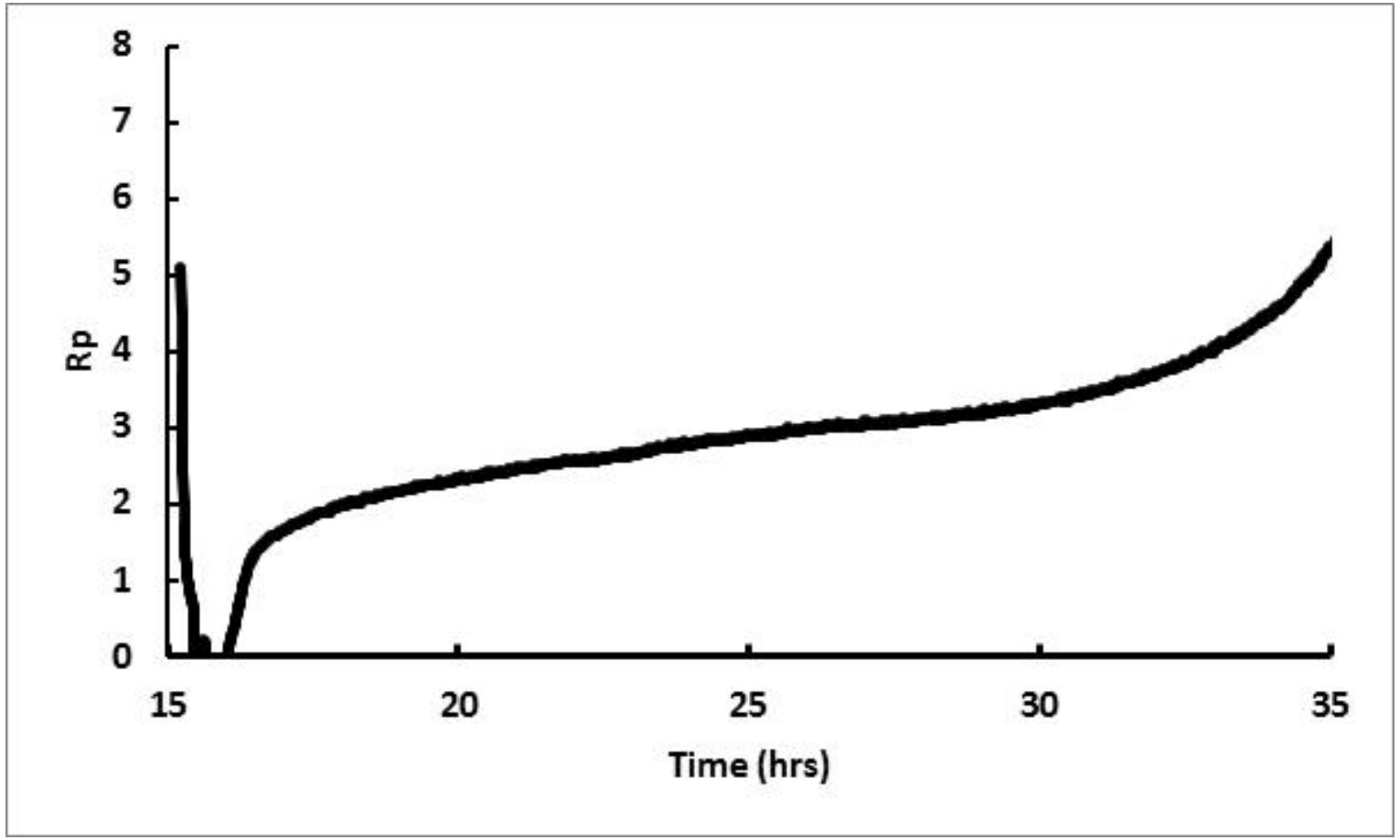
where

$$P_i \text{ (in Torr)} = 2.698 \times 10^{10} \exp(-6144.96/T_b)$$

Example of Process Data for Rp Determination



Example of Product Resistance Data



Construct Shelf Temperature and Product Temperature Isotherms

1. Choose an arbitrary value for T_s and P_c
2. Calculate the corresponding values of T_b and dm/dt

$$\frac{DH_s A_p (P_i - P_c)}{R_p} = K_v A_v (T_s - T_b)$$

or,

$$\{DH_s A_p [2.698 \times 10^{10} \exp(-6144.96/T_b) - P_c]\}/R_p = K_v A_v (T_s - T_b)$$

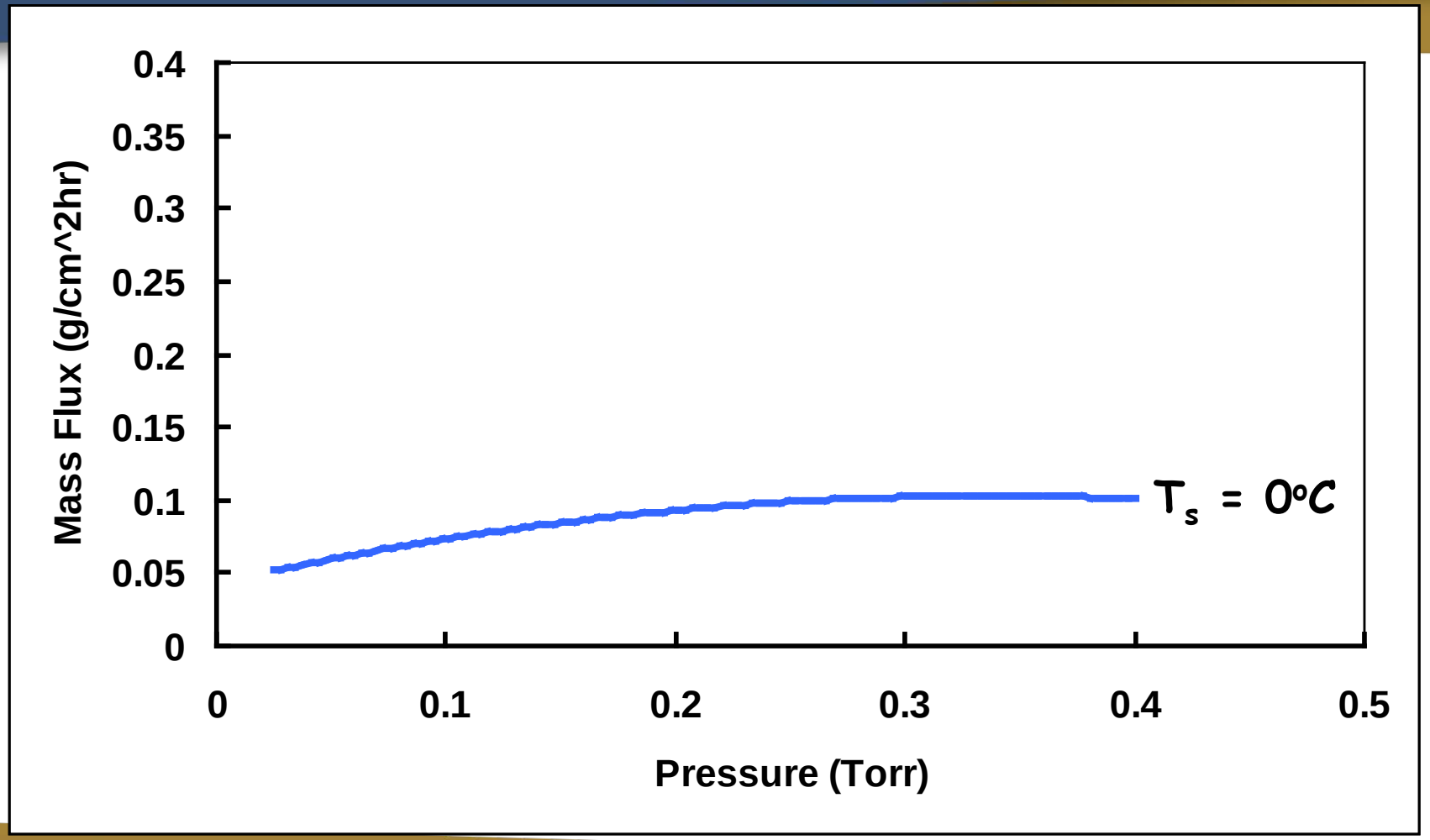
Solve this iteratively for T_b

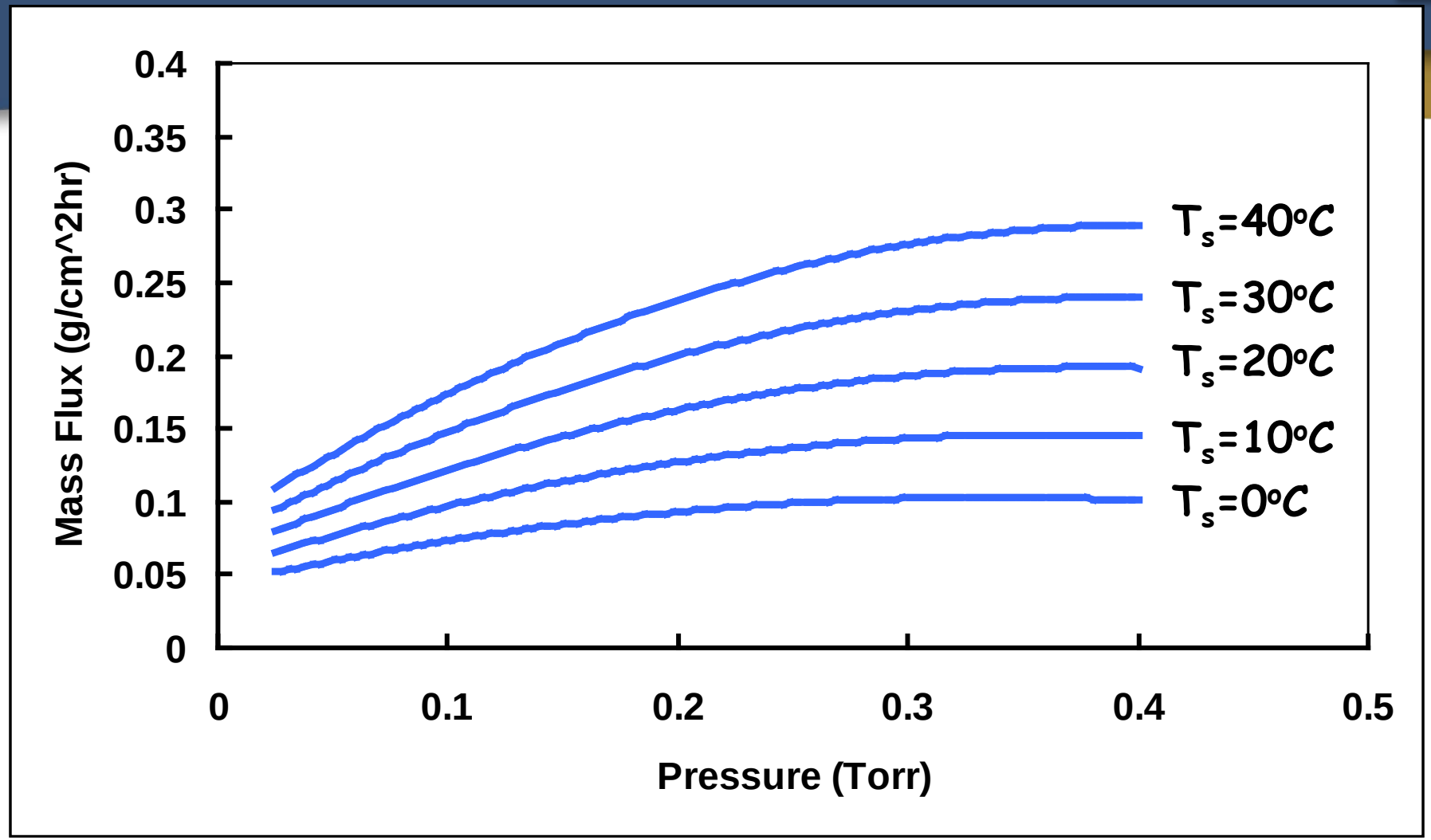
Design Space Calculations (continued)

3. Now calculate the corresponding mass flow rate by

$$dm/dt = K_v A_v (T_s - T_b)$$

4. Now choose a new value of P_c at the same T_s
5. Repeat this process for several values of P_c. The resulting plot of mass flow rate vs. pressure generates one shelf temperature isotherm.


0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Mass Flux (g/cm^2hr)
0
0.1
0.2
0.3
0.4
0.5
Pressure (Torr)
T_s = 0°C


0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Mass Flux (g/cm^2hr)
0
0.1
0.2
0.3
0.4
0.5
Pressure (Torr)
Ts=40oC
Ts=30oC
Ts=20oC
Ts=10oC
Ts=0oC

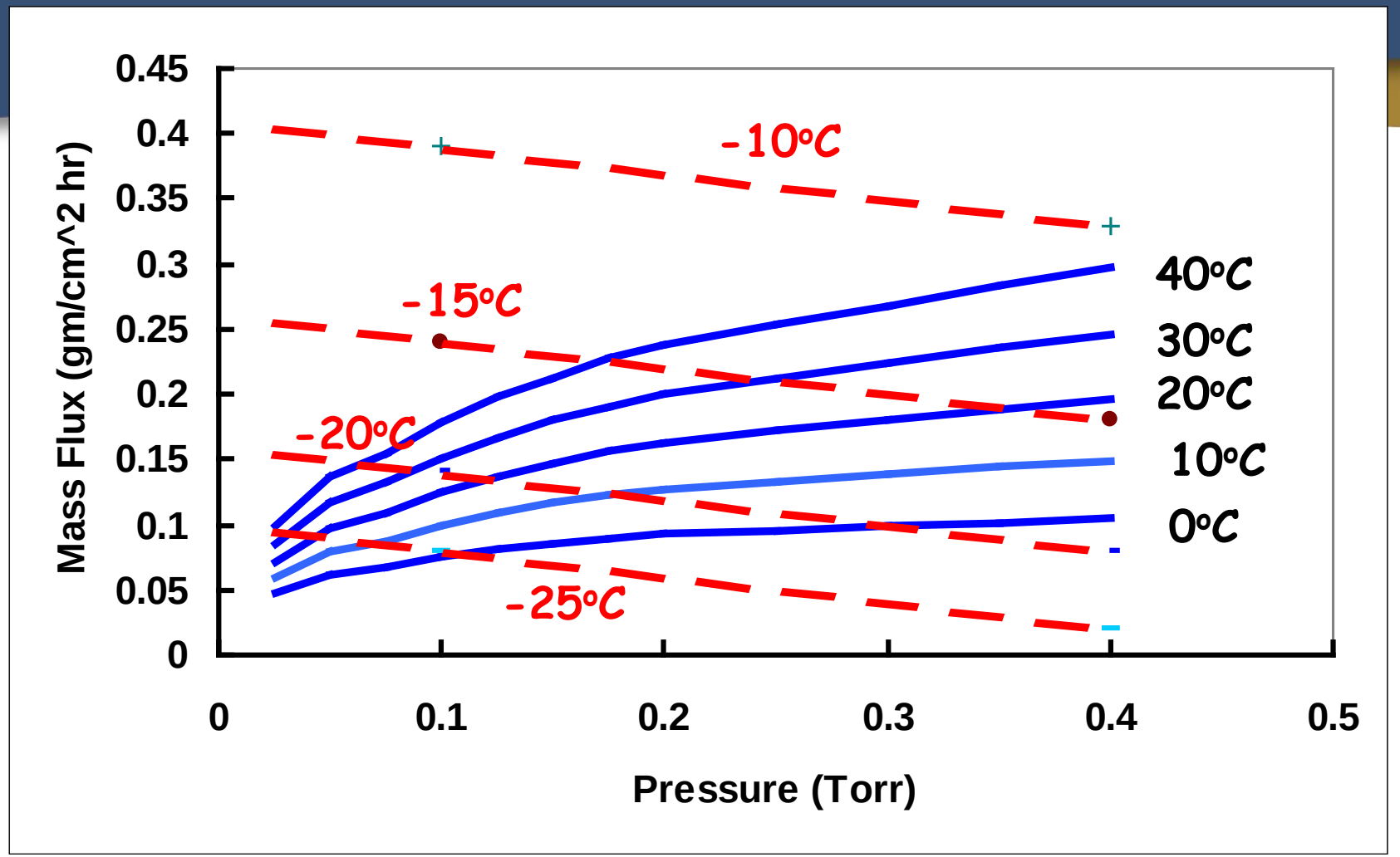
Design Space Calculations (continued)

Generate the product temperature isotherms by choosing an arbitrary product temperature, T_b, and a chamber pressure, P_c.

Calculate the sublimation rate under these conditions by

$$dm/dt = A_p \frac{[2.698 \times 10^{10} \exp(-6144.96/T_b) - P_c]}{R_p}$$

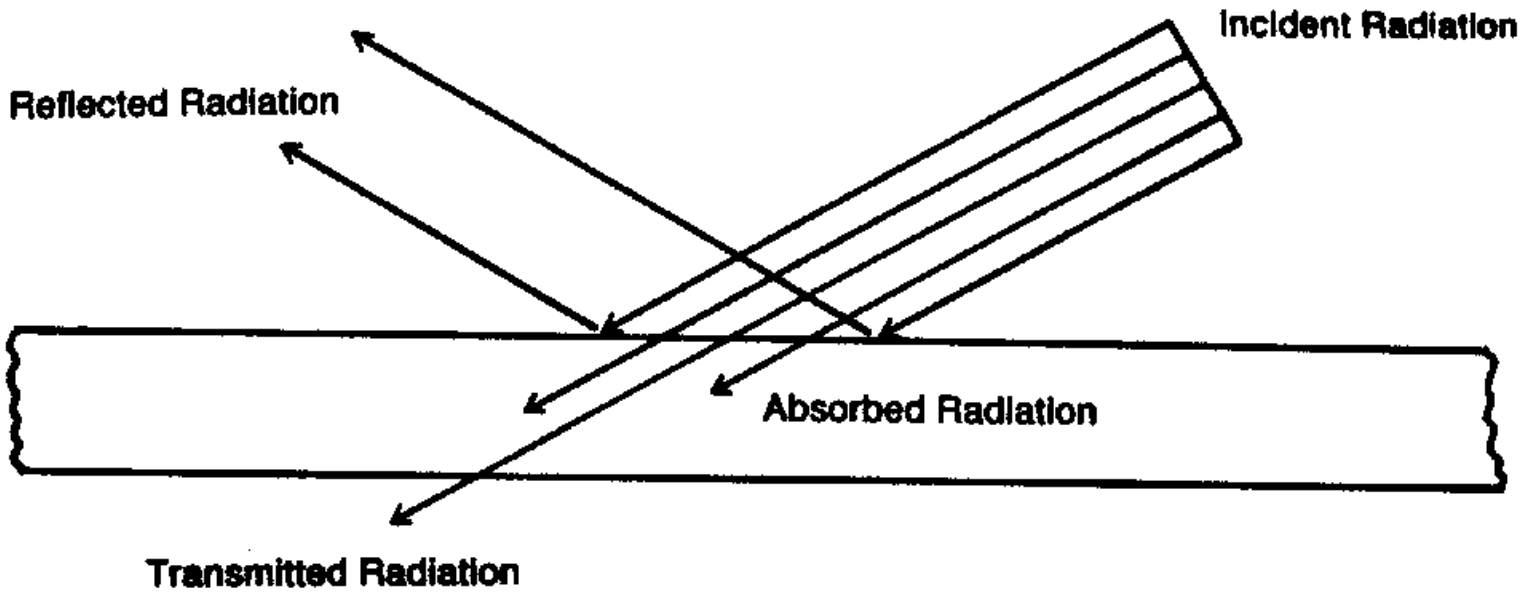
Note: The product temperature isotherms are linear, so only two pressures are needed for each value of T_b


0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Mass Flux (gm/cm^2 hr)
0
0.1
0.2
0.3
0.4
0.5
Pressure (Torr)
-10°C
-15°C
-20°C
-25°C
40°C
30°C
20°C
10°C
0°C

Note:

- Both K_v and R_p are batch average values. They are not necessarily the same from vial to vial.
- The “edge effect” is particularly significant.

Heat Transfer by Thermal Radiation



Stefan-Boltzman Law

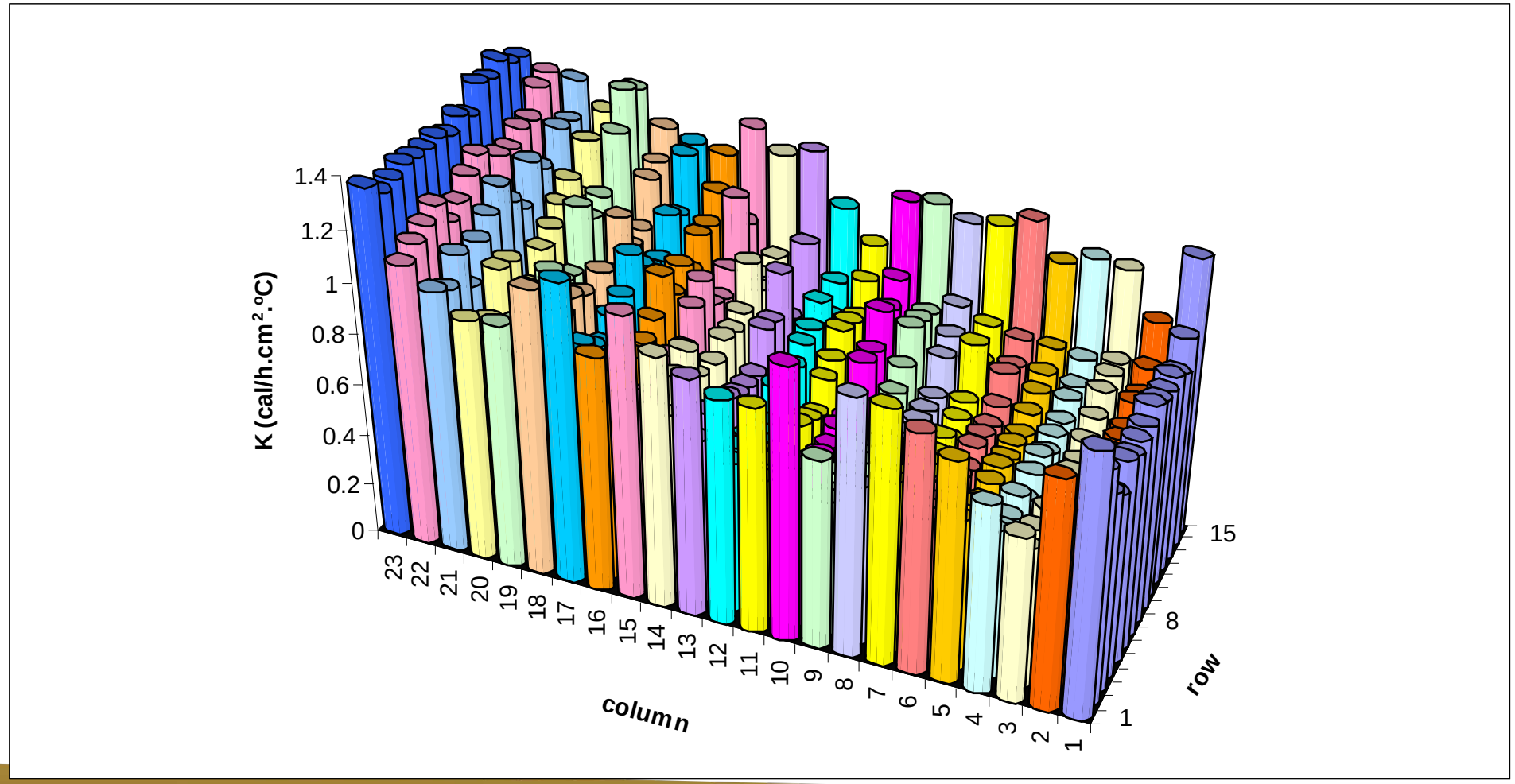
$q = \sigma T^4$ for blackbody

$q = \sigma \varepsilon T^4$ for graybody

Heat Transfer by Thermal Radiation Depends On:

- Temperature
- Thermal emissivity of materials

Sublimation Rate Mapping for Lab Freeze-Dryer

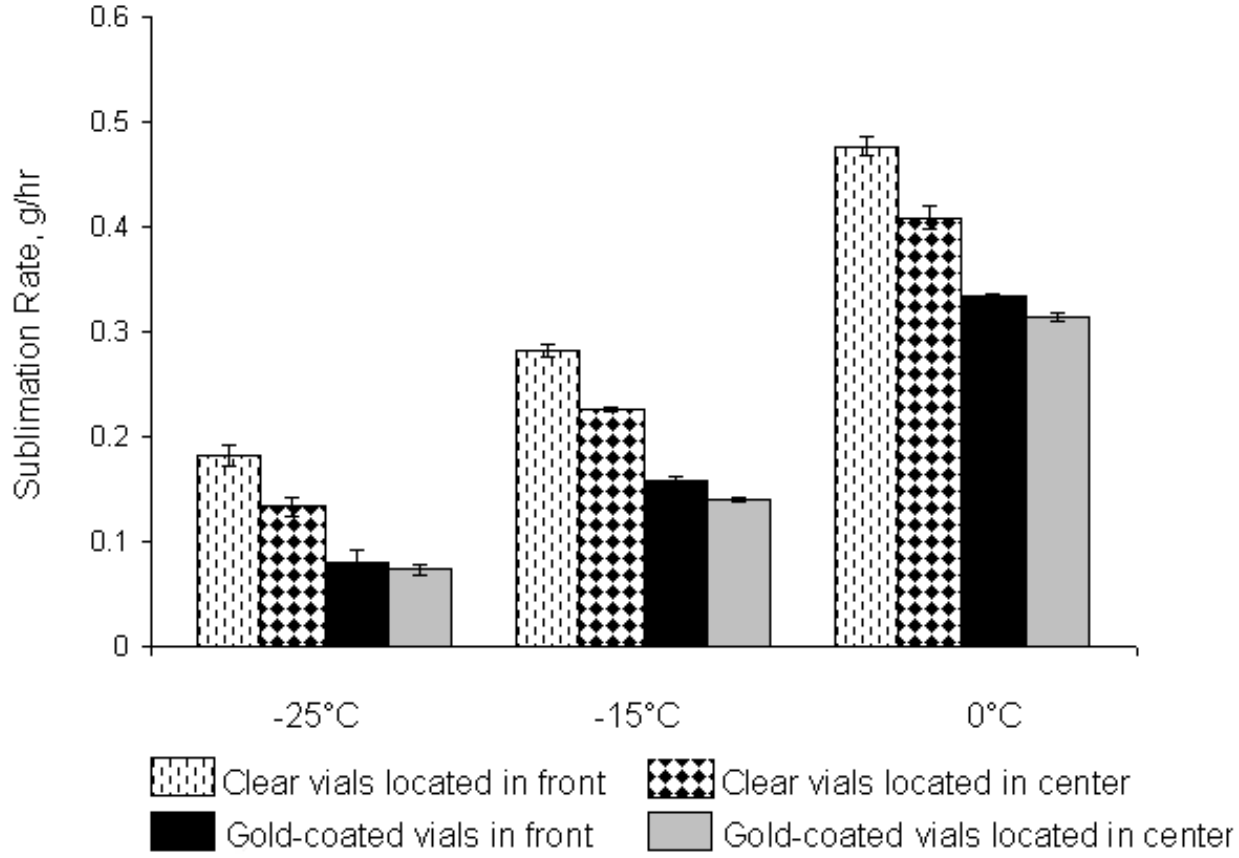


The “Edge Effect”

Reference: Rambhatla and Pikal,

The “Edge Effect”

Reference: Rambhatla and Pikal,



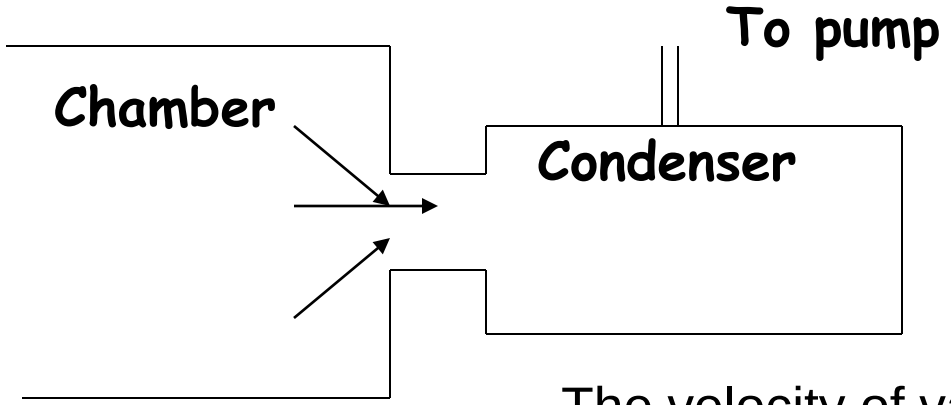
Other Sources of Uncertainty in this Approach

- It assumes a constant shelf temperature during primary drying
- Demand for equipment capability is highest early in primary drying, but risk to product is greatest late in primary drying.

Next Step: Add the Equipment Capability Curve

- Any freeze dryer has a limit to the sublimation rate that it will handle. It is very important to understand equipment capability, both at the laboratory and the production scale
- Factors that can limit performance
  - Refrigeration capacity
  - Condenser surface area
  - Upper limit of shelf temperature
  - Dynamics of vapor flow from chamber to condenser

Dynamics of Vapor Flow as a Limiting Factor in Equipment Capability



The velocity of vapor through the “throat” of the system is limited by the speed of sound in that vapor stream. This Is called “choked flow.”

Measuring the Equipment Capability Curve

- Two methods can be used. Both are done with ice slabs covering the entire shelf area

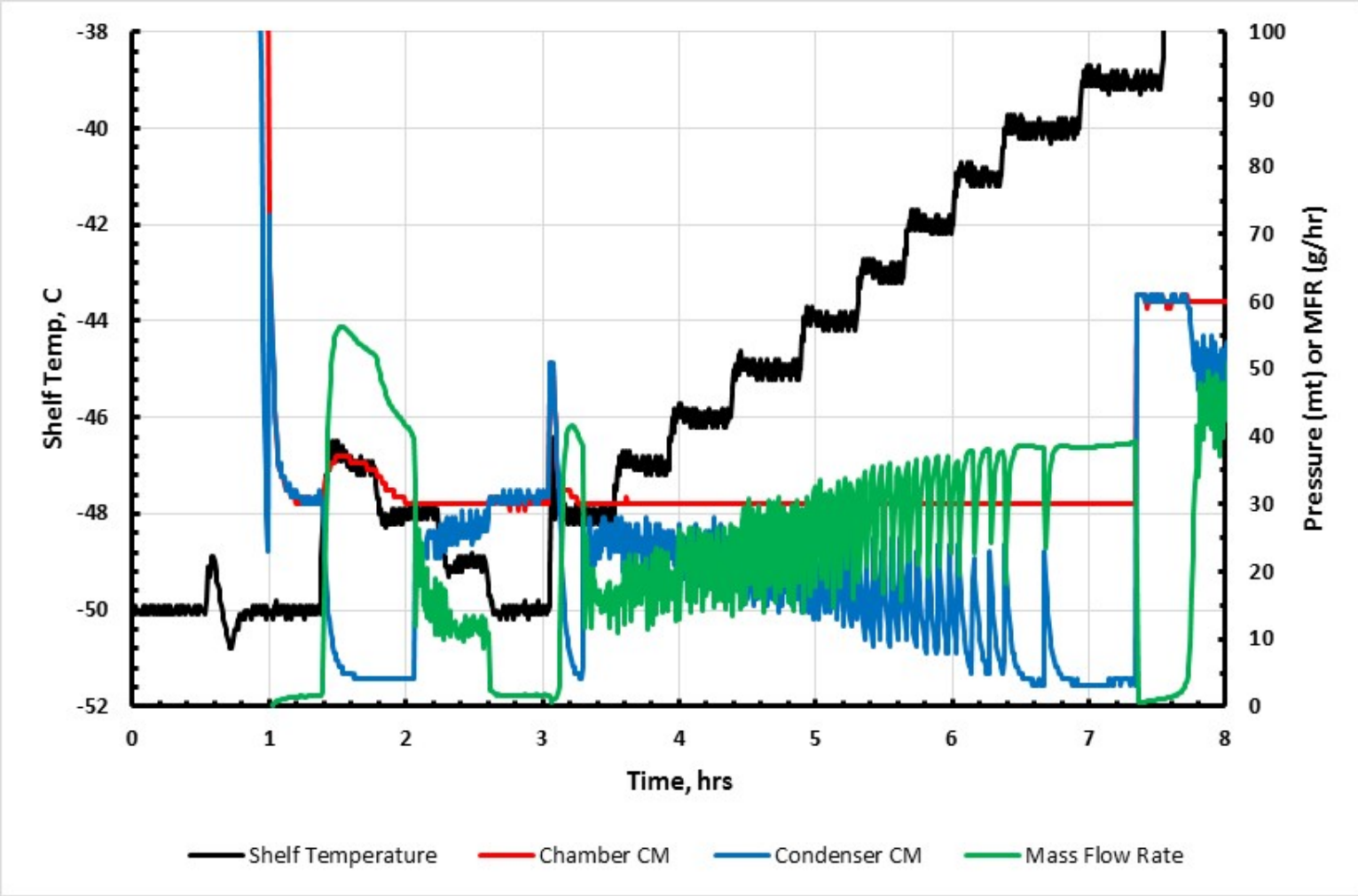
Measuring the Equipment Capability Curve

- Choke Point Method
  - Pour a known quantity of water into each lined tray ring.
  - Freeze ice slabs overnight to, say, -50°C
  - Evacuate system to low end of pressure range – say 30 mT
  - Once steady state is established at the pressure set point, make stepwise increases in shelf temperature until the pressure exceeds the set point. This is the choke point at that pressure. Note the mass flow rate of water vapor (we use TDLAS). If available, also note the condenser pressure.
  - Establish a new pressure set point, let the system reach steady state, then continue making step changes in shelf temperature until the pressure exceeds this set point.
  - Continue this process until the pressure range of interest has been covered.
  - Note the mass of ice remaining after the test. Compare with the TDLAS total.

Measuring the Equipment Capability Curve

- Minimum Controllable Pressure
  - Pour a known quantity of water into each lined tray ring.
  - Freeze overnight at, say, -50^{o}C.
  - Evacuate the system and set chamber pressure set point at some value below system capability – perhaps 10 mT.
  - Allow system to reach steady state and record mass flow rate of water vapor. This flow rate corresponds to the minimum controllable pressure at that shelf temperature. If available, also note the condenser pressure.
  - Make stepwise changes in the shelf temperature, allow steady state to be established, and record the mass flow rate corresponding to each shelf temperature.
  - Make sure that the pressure set point on the TDLAS corresponds to the pressure set point on the freeze dryer.

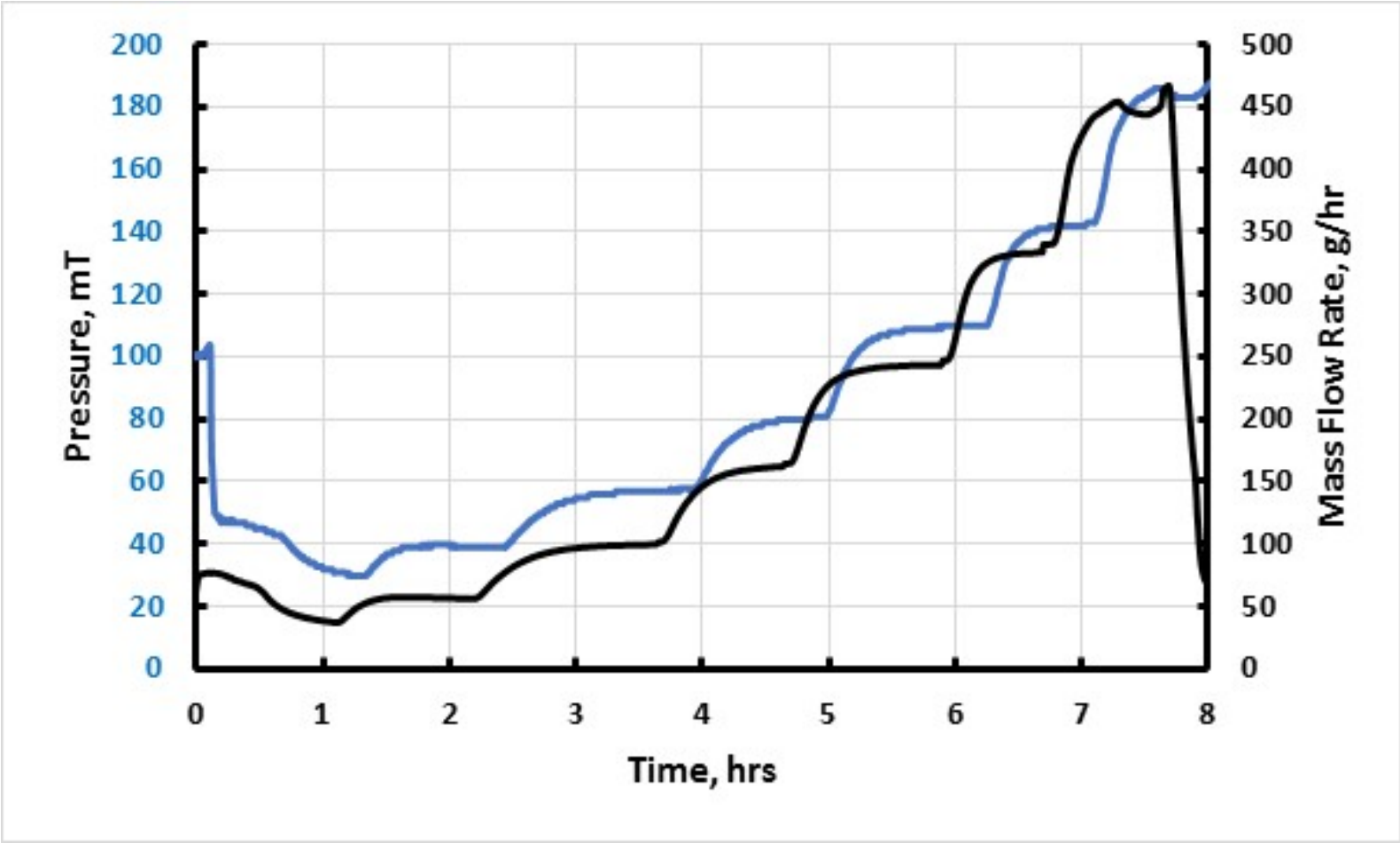
Representative Data – Choke Point



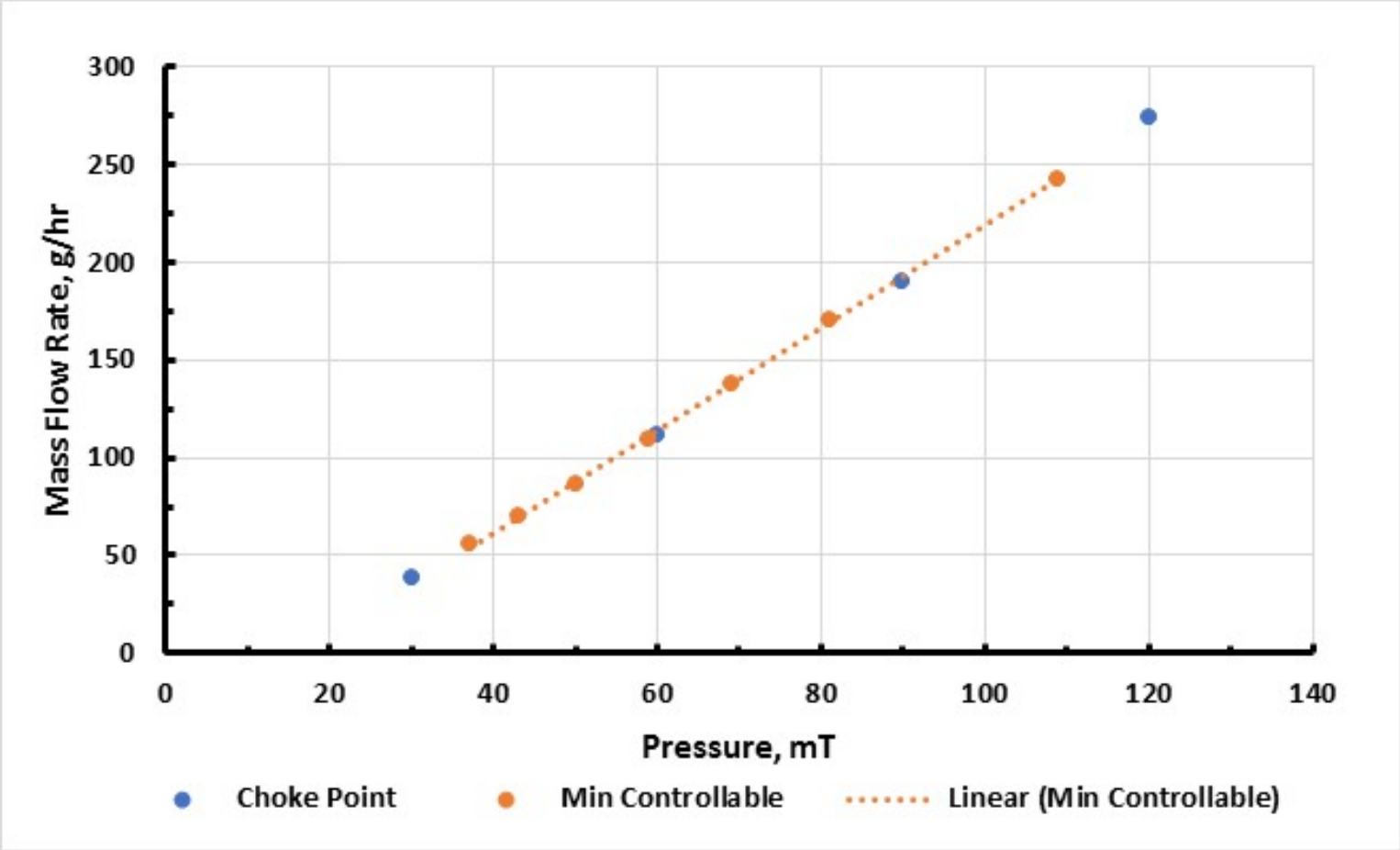
Representative Data – Choke Point

When the condenser pressure “bottoms out”, with no spikes, the mass flow rate reaches steady state – in this case, at 38.3 g/hr. This corresponds to a shelf temperature of -40^{o}C. Note also that the chamber pressure is still under control at this point. We then establish a new pressure set point and continue to make step changes in shelf temperature until we’ve covered an adequate pressure range.

Representative Data – Min Controllable Pressure



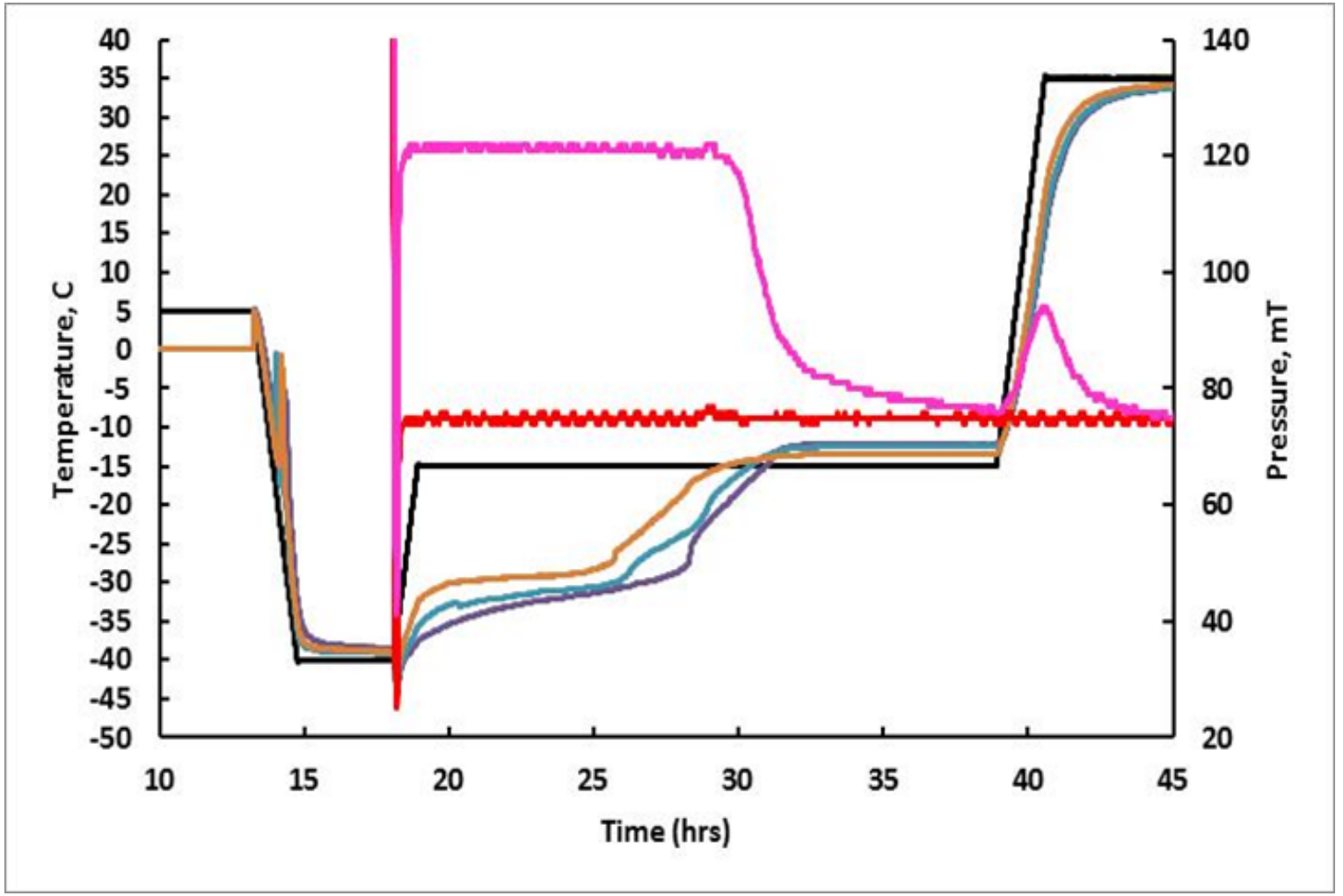
Summary


300
250
200
150
100
50
0
Mass Flow Rate, g/hr
0
20
40
60
80
100
120
140
Pressure, mT
Choke Point
Min Controllable
Linear (Min Controllable)

A Note About Equipment Capability

- The relationship between the controlled variables (shelf temperature and chamber pressure) and product temperature is typically established on laboratory scale freeze dryers.
- The relevant equipment capability curve, however, is the equipment that will be used for drug product manufacture. There is a need, across the industry, for better information on capability of production scale freeze dryers.

Secondary Drying



Secondary Drying (continued)

- Both published data and our own unpublished data show that neither the rate nor the extent of secondary drying are affected by chamber pressure. This is probably because the rate-limiting step is the diffusion of water molecules through the glassy matrix.
- This can be useful in making good decisions regarding the disposition of product when a pressure deviation happens during secondary drying.