Scale-Up and Tech Transfer: ABCs and Beyond

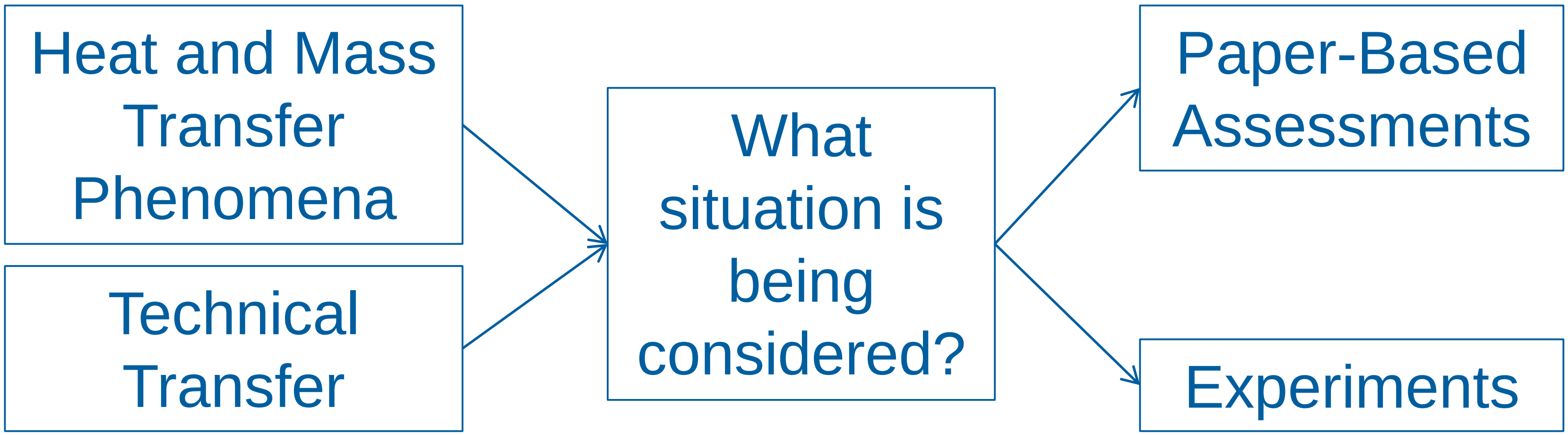
Jim Searles, Ph.D.
Technical Fellow
Manufacturing Science and Technology
Hospira and One 2 One Contract Manufacturing

KNOWLEDGE | EXPERIENCE | EXPERTISE

2015 AAPS NBC, Short Course on Lyophilization
June 11 2015

Outline

1. Introduction
2. Heat and Mass Transfer Phenomena
3. Technical Transfer
4. Paper-Based Assessments
5. Experiments

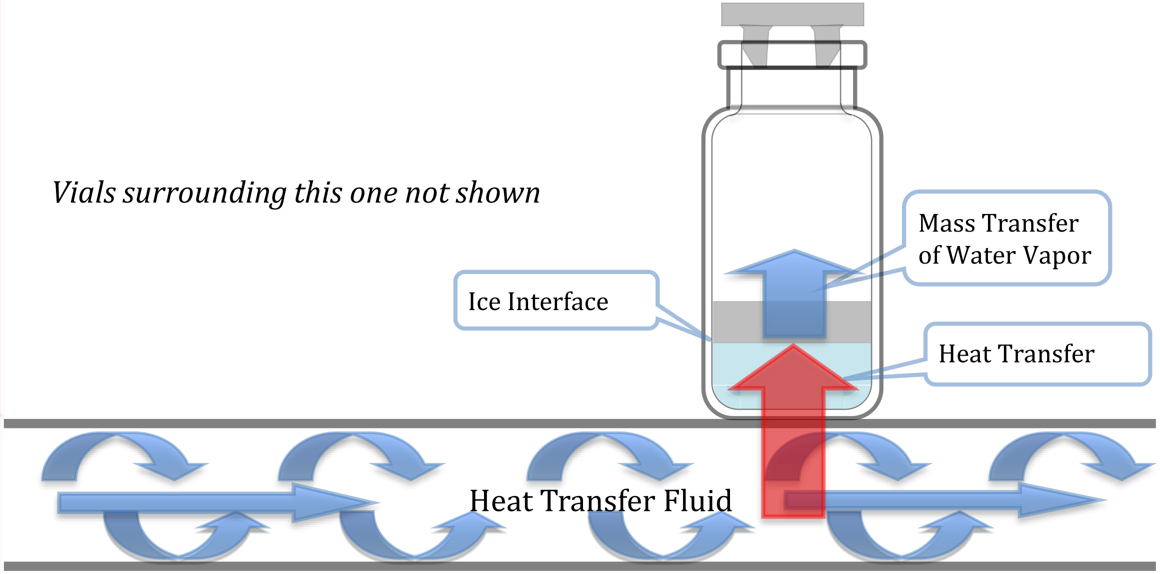

Heat and Mass Transfer Phenomena
Technical Transfer
What situation is being considered?
Paper-Based Assessments
Experiments

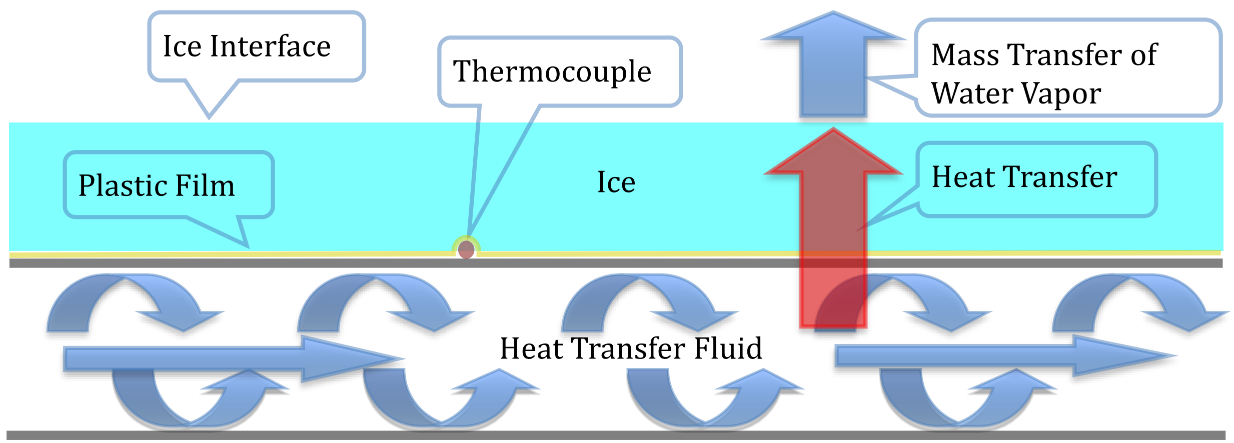
Definitions

- Scale-Up
  - Increase the extent of lyophilizer loading
  - Increase of lyophilizer size
  - *Done as part of most tech transfers*
- Technical Transfer
  - Moving from one commercial mfg site to another
  - Moving from R&D -> Clinical/Pilot -> Commercial mfg
    - *Also includes scale-up*
    - *Also includes improvements in the lyo cycle, and establishment of acceptable process parameter ranges*

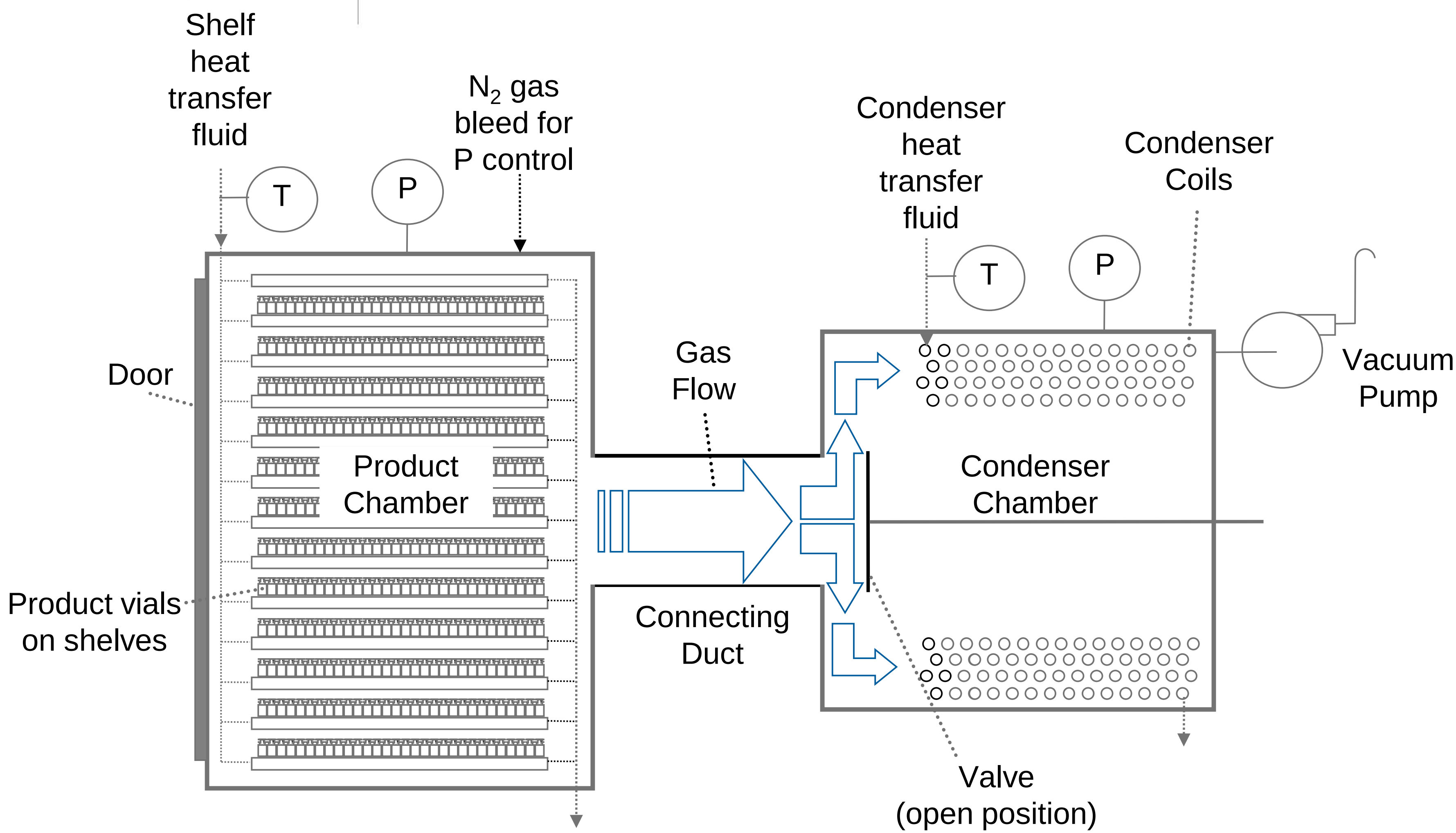
HEAT AND MASS TRANSFER

Vials surrounding this one not shown





Large-Scale


Shelf heat transfer fluid
T
P
N2 gas bleed for P control
Door
Product Chamber
Product vials on shelves
Gas Flow
Connecting Duct
Condenser heat transfer fluid
T
P
Condenser Coils
Vacuum Pump
Condenser Chamber
Valve (open position)

Increased Extent of Loading

- Always a factor:
  - Thermal radiation heat transfer distributed over a larger number of vials
    - This is a minor effect
    - Primary drying: Lower product T's, slower primary drying
- Observed in some cases:
  - Unable to hold pressure set point due to choked flow or condenser overload
  - Slower secondary drying
  - Higher residual moisture
- Other possibilities to consider:
  - Slower shelf ramps due to higher thermal load
  - Effects of longer loading and unloading times

Thermal Gradients in Lyophilizers

- Post-SIP re-cooling is not perfect
  - Not re-cooled: force distribution structure at the top of the dryer, above the shelf stack
  - Lyo walls are usually re-cooled after SIP
    - Do not take for granted that it is sufficient!
- Before vacuum is pulled, hot air rising causes a top-to-bottom temperature gradient in the dryer
- After vacuum is pulled, thermal radiation continues to emit from the warmer structures at the top of the dryer, preferentially affecting the higher shelves

Extent of Loading 2

- Loading usually begins with the top shelf
- Increasing the extent of loading means that the additional vials load on progressively lower shelves
- Lower shelves are a slightly “cooler” environment

Primary Drying Effects

Table 6. Effect of Gas Composition on Product Temperature and Primary Drying Time (10 cc, 13 mm Tubing Vials), 5% Sucrose, Primary Drying at −25°C, 60 mTorr).

Gas Composition, X_w	K_v (cal/cm^2 s K)	T_p (°C)	T_{dry} (h)
1.00	4.27	−35.6	17.8
0.77	4.17	−35.7	18.1
0.00	3.76	−36.1	19.3

Heat transfer *via* gas conduction was calculated using Eqs. (4), (8), and (9). The vial heat transfer coefficient was then calculated from Eq. (3). Further, the steady-state theory of heat and mass transfer was used to compute product temperature and drying time as described in the text.

Table 10. Comparison of Primary Drying Time (h) as Determined from the Sharp Drop in the Pirani Pressure for 5% Mannitol at Different Load Conditions on a Lab, Pilot and Clinical Scale Dryer

% Load	Lab Scale	Pilot Scale	Clinical Scale
100	8.5	8.8	10.6
50	7.8	7.7	N/A
10	7.3	7.2	9.5
2	6	5.5	N/A

S. Patel et al. Journal of Pharmaceutical Sciences, Vol. 99, 4363–4379 (2010)

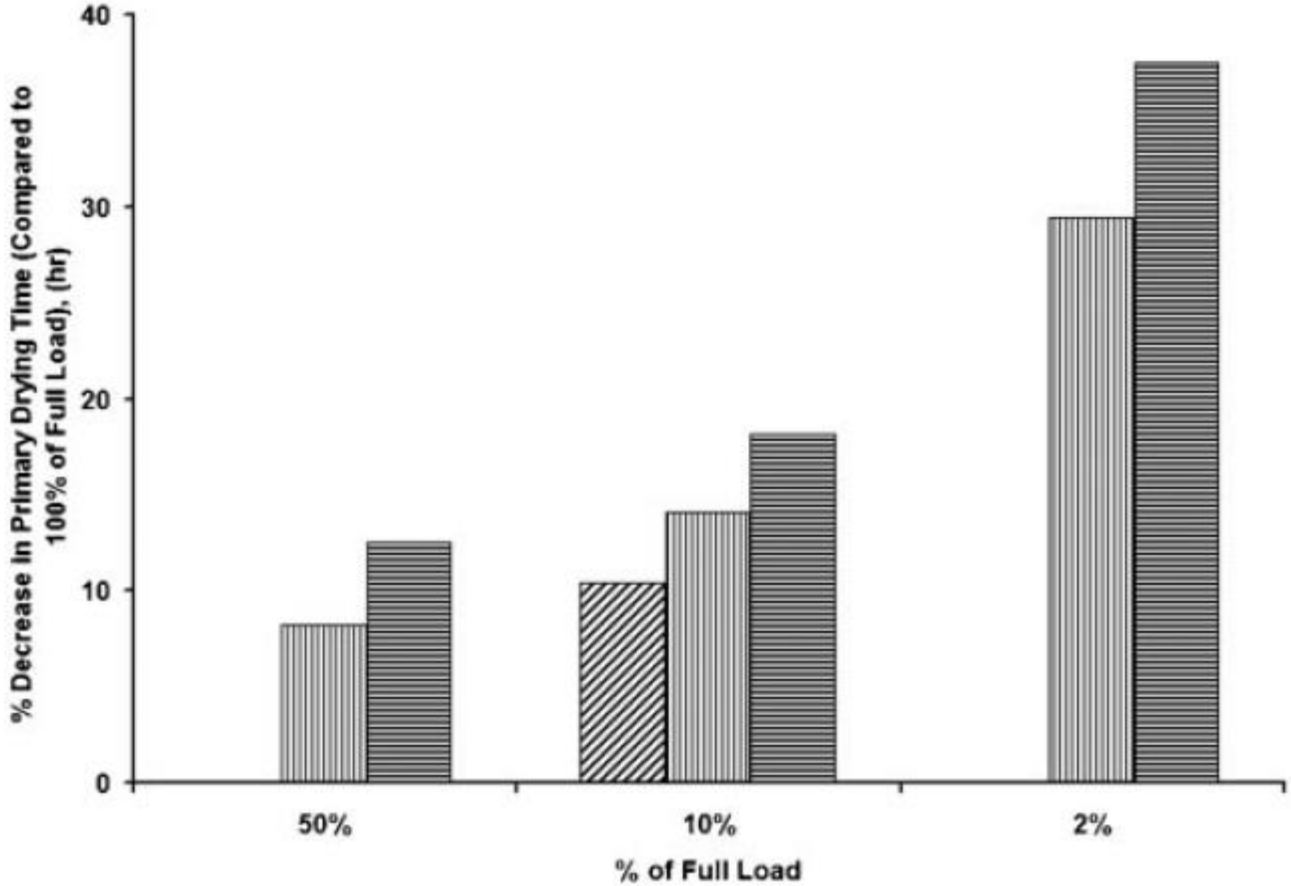


Figure 7. % decrease in primary drying time compared to 100% of full load for 5% mannitol under different partial load conditions. Key: vertical stripes = lab scale, horizontal stripes = pilot scale, and diagonal stripes = clinical scale. Drying time determined from the sharp decrease in Pirani pressure for lab, pilot, and clinical scale at 100% load is 8.5, 8.8, and 10.6 h, respectively.

S. Patel et al. Journal of Pharmaceutical Sciences, Vol. 99, 4363–4379 (2010)

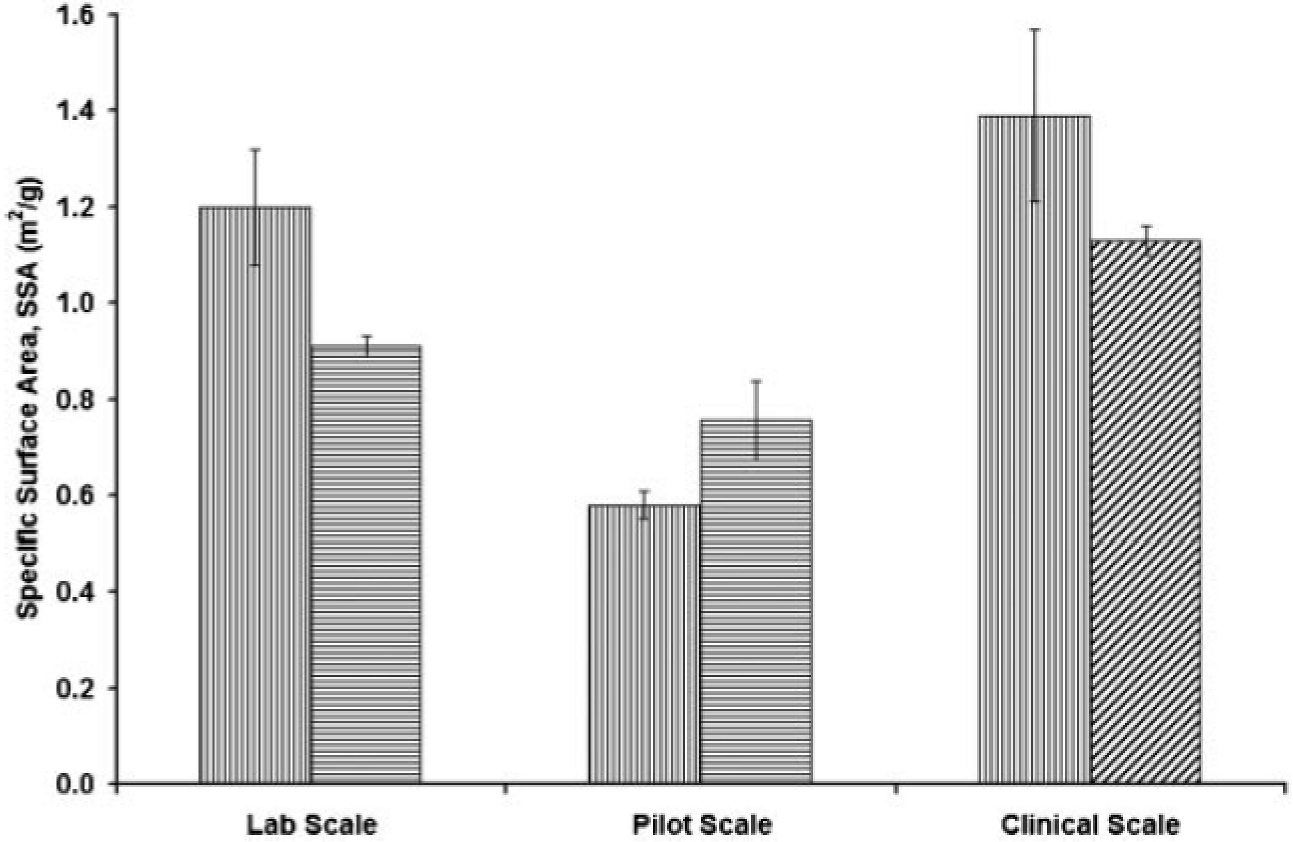
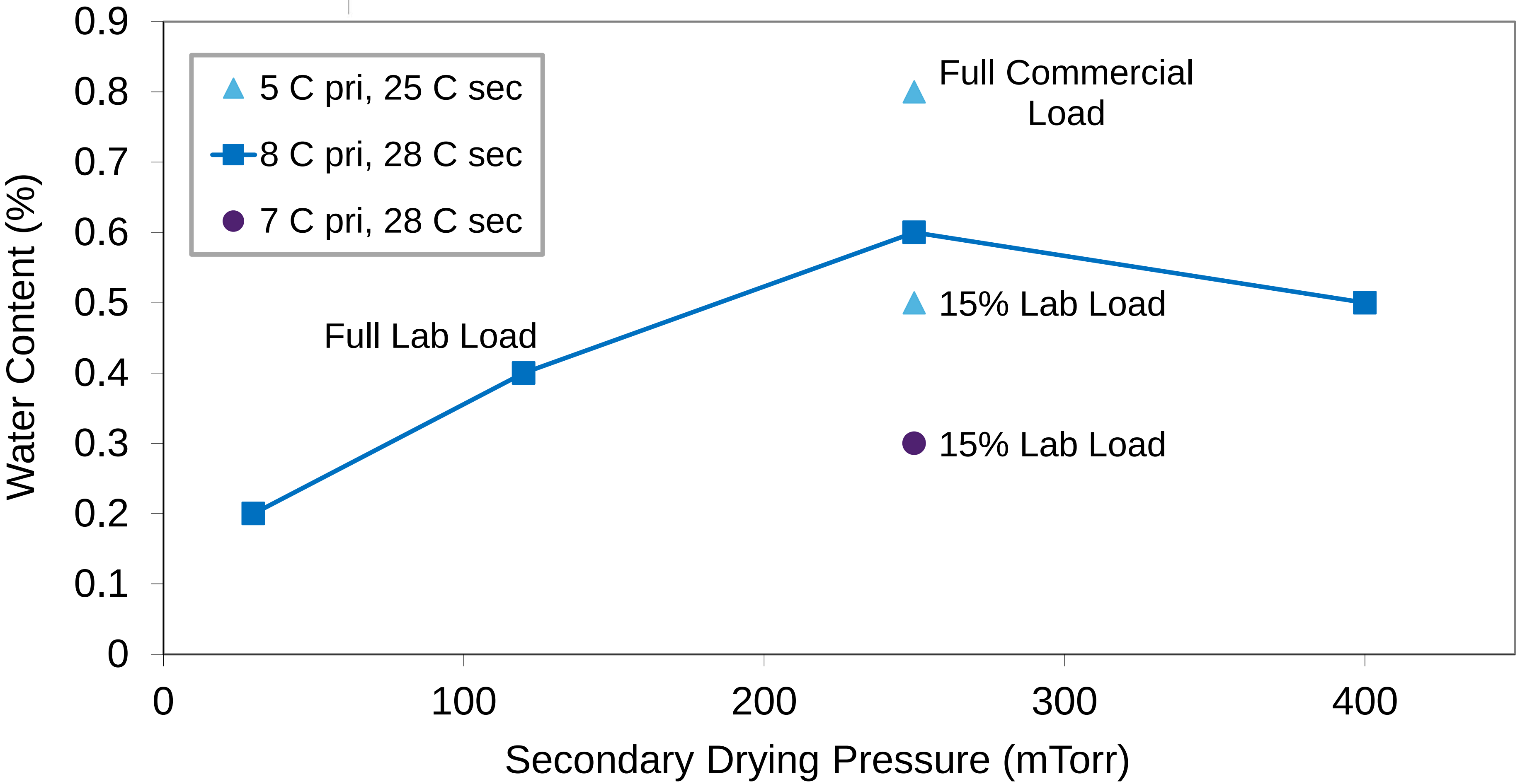


Figure 9. Comparison of specific surface area for center and edge vials under different load conditions for 5% sucrose on a lab scale, pilot scale and clinical scale dryer. Key: vertical stripes = 100% of full load, horizontal stripes = 2% of full load, and diagonal stripes = 10% of full load. Error bars are standard deviations for $n = 3$, but also represent approximately the 90% confidence limit.

S. Patel et al. Journal of Pharmaceutical Sciences, Vol. 99, 4363–4379 (2010)

Extent of Loading



250 mTorr CM primary drying for 46 hours; 28 C shelf secondary drying for 6 hours

Secondary Drying Effect

On a production scale dryer with a full load, a drying time of about 240 min resulted in residual moisture of < 1 %. However, at 25 % of full load, residual moisture dropped to < 1 % in 200 min. Overall, there was not much effect of load on secondary drying and, hence, drying time was fixed at 300 min as a contingency option in the event that Pirani and TDLAS failed to monitor and control the process.

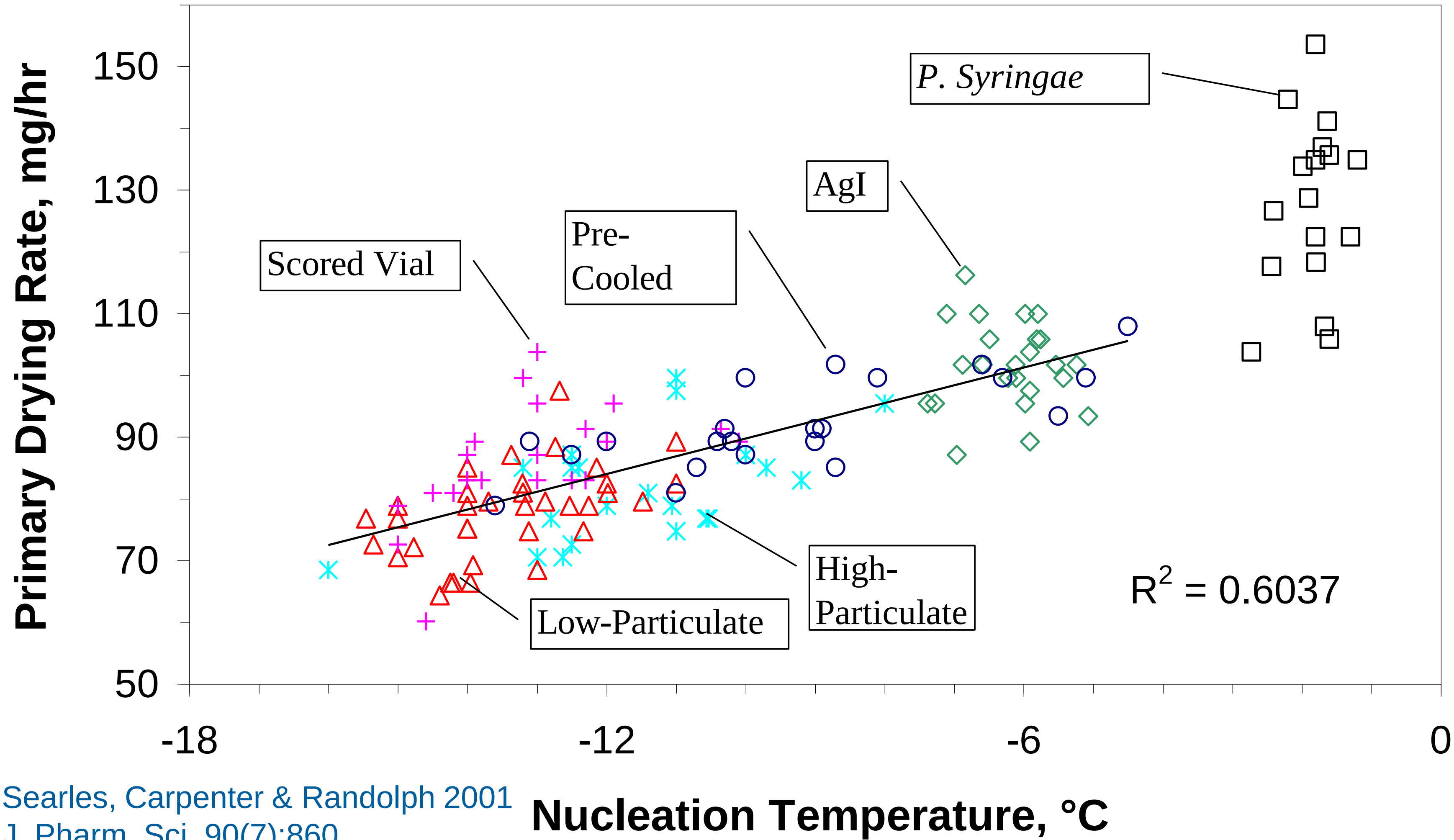
S. Patel et al. 2015. Chapter 14- Lyophilization Process Design and Development Using QbD Principles in F. Jameel et al. (eds.), Quality by Design for Biopharmaceutical Drug Product Development, AAPS Advances in the Pharmaceutical Sciences Series 18, DOI 10.1007/978-1-4939-2316-8_14

TECHNICAL TRANSFER

Moving from R&D -> cGMP MFG

- Lower ice nucleation temperatures in cGMP mfg
  - Cleaner conditions, less particulate that can act as ice nucleation sites
  - Results in smaller ice crystals, slower drying at higher product temperatures
- Higher vial breakage rates in commercial mfg
  - Depyrogenation and conveying damage the vials
  - Breakage during lyo not uncommon

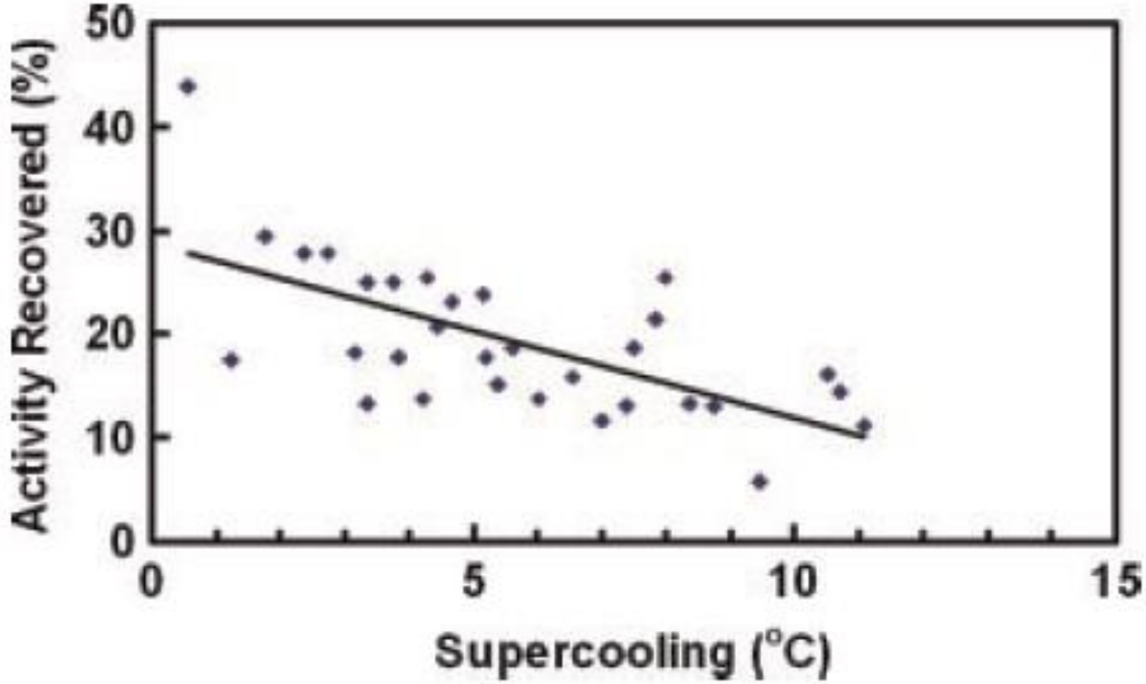
Effect of Nucleation T



Searles, Carpenter & Randolph 2001
J. Pharm. Sci. 90(7):860

Nucleation T can also affect product quality

- Lactate dehydrogenase activity affected by the ice nucleation temperature
- Protein adsorption to the ice interface?



Cochran and Nail (2009) J. Pharm Sci. 98(9):3495

Nakagawa 2006 Chem. Eng. and Processing 45:783

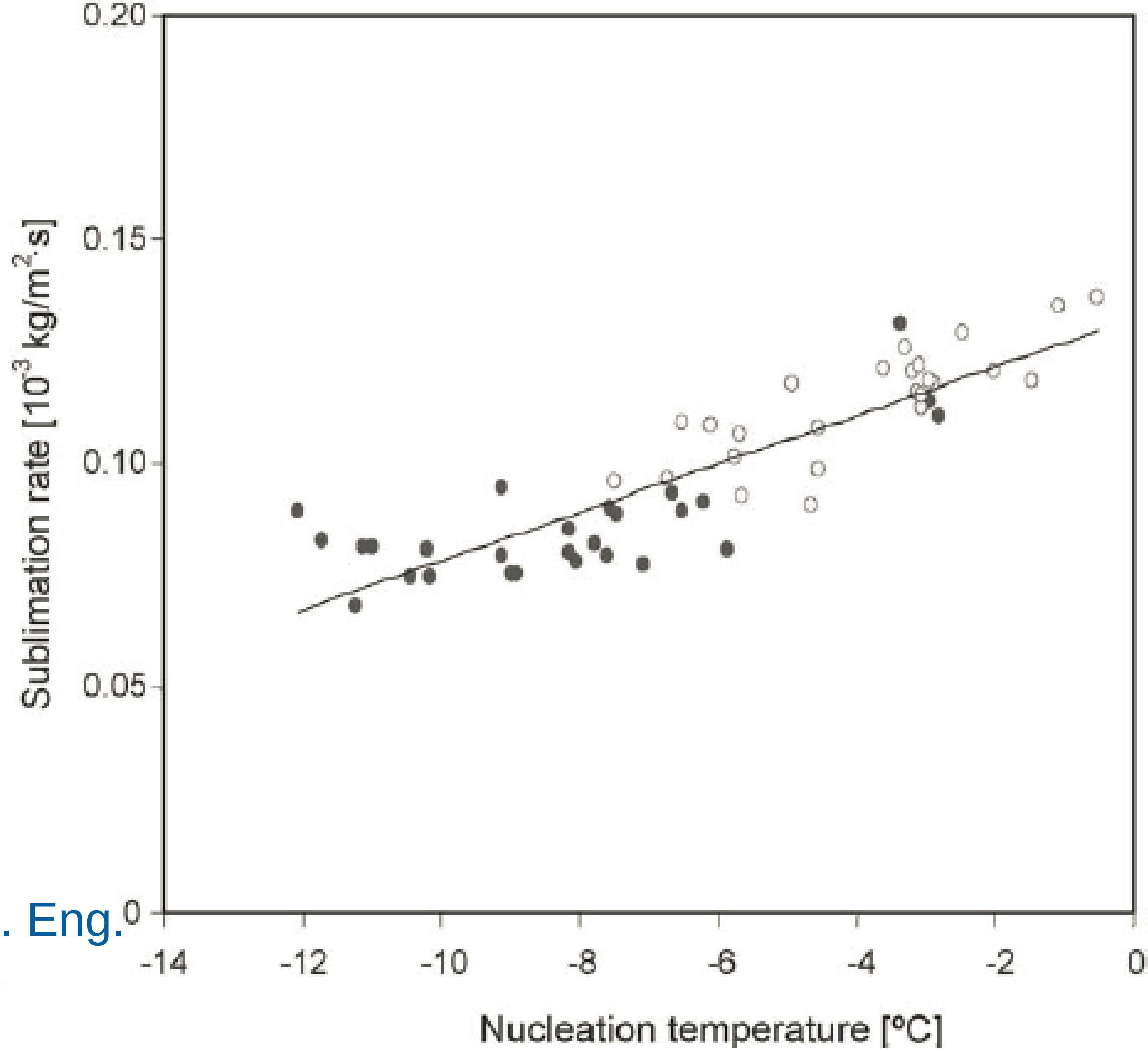


Fig. 12. Primary drying rates versus nucleation temperatures (10% sucrose). Open symbol: controlled nucleation by ultrasound; closed symbol: spontaneous nucleation.

Technical Transfer

- Change in equipment
  - Understand the differences (may require experiments to characterize)
- Moving further through the product life-cycle
  - Full QbD development requires extensive laboratory characterization of the product and the lyophilization cycle
  - Define Proven Acceptable Ranges (PARs) in time for initial Process Qualification

PAPER-BASED ASSESSMENTS

Information Gathering

- Operational Parameters
  - Temperatures and pressures
  - Heating, cooling, and vacuum rates
  - Shelf heat transfer coefficient
- Dimensions
  - Connecting duct cross-sectional area in relation to shelf surface area
  - Condenser coils/plates surface area in relation to shelf surface area
- Controls

	LyoStar™	Edwards™
Condenser (external)		
Capacity	30 L	548 L
Surface area	7 ft^2 (0.65 m^2)	301 ft^2 (28 m^2)
Temperature	−85 °C	−80 °C
Chamber		
Shelf dimensions	11 in. × 20 in. (28 cm × 51 cm) 1.53 ft^2 per shelf 3 Shelves = 4.59 ft^2	48 in. × 60 in. (122 cm × 152 cm) 20 ft^2 per shelf 11 Shelves = 220 ft^2
Opening to condenser	3.75 in. (9.525 cm)	24 in. (60.96 cm)
Ratio of condenser surface area to shelf surface areas		
7 ft^2/4.59 ft^2	1.525	
301 ft^2/220 ft^2		1.368
Ratio of shelf area to condenser opening area		
4.61 $ft^2/3.14 \times (0.3125)^2/4$	60.2	
219.57 $ft^2/3.14 \times (2.0)^2/4$		69.9

W.Y. Kuu et al. / International Journal of Pharmaceutics 302 (2005) 56–67

Properties	A	B	C
Capacity of the condenser, kg	40	120	600
Surface area of the condenser, m^2	0.38	2.00	25.00
Surface area of the shelves, m^2	0.64	3.35	40.50
Ratio between condenser and shelf surface area	0.59	0.60	0.62

Pisano et al. 2013, AAPS PharmSciTech DOI: 10.1208/s12249-013-0003-9

Table 1. Basic Characteristics of Lyophilizers*

	Laboratory (KTS)		Pilot	Manufacturing	
Characteristics	Durastop	Lyostar I	Lyofast (Edwards)	Lyomax (Edwards)	Stokes
Total shelf surface, m^2	0.38	0.35	2	39	24.2
Condenser surface, m^2	0.64	0.37	2	43	24.6
Chamber to condenser pathway	D = 0.05	D = 0.1	D = 0.25	D = 0.91	D = 0.9
	L = 0.27	L = 0.48	L = 0.75	L ≈ 1.5	L = 0.9

*D and L are the diameter (m) and length (m) of the chamber to condenser pathway, respectively. KTS indicates Kinetics Thermal Systems.

Rambhatla et al., AAPS PharmSciTech 2006; 7 (2) Article 39

EXPERIMENTS

Experiments

	Laboratory	Production
Drying rate capability vs pressure	√	√
Shelf heat transfer coefficients	√	√
Product drying rate	√	
Basic lyo cycle development	√	
Proven Acceptable Range testing	√	
Edge of failure testing	√	
Evaluate specific process deviations	√	

Approach

Use lab lyophilizers as “scale-down” models to:

- Develop a cycle that will work in commercial manufacturing lyophilizers with minimal change in quality attributes
- Cycle should be as short as possible
- Generate Proven Acceptable Ranges (PAR’s) for production scale to allow “space” for all of the factors discussed in this presentation
    - +/- 2 C and +/- 20 mTorr for all of the drying steps (HH and LL discussed further later)
- Test the effect of process deviations

Heat Transfer Efficiency

Vial location	Vial heat transfer coefficient, K_v ($\times 10^4$ cal/cm^2 s K)	
	Lab scale dryer	Production scale dryer
Edge	3.24 ± 0.08	2.85 ± 0.04
Center	2.15 ± 0.03	1.69 ± 0.03

S. Patel et al. 2015. Chapter 14- Lyophilization Process Design and Development Using QbD Principles in F. Jameel et al. (eds.), Quality by Design for Biopharmaceutical Drug Product Development, AAPS Advances in the Pharmaceutical Sciences Series 18, DOI 10.1007/978-1-4939-2316-8_14

Lyophilizer	K_s*10^3, cal.$s^{-1}cm^{-2}.K^{-1}$ Calculated From Slope
Laboratory (Lyostar I)	5.4 ± 1.9
Laboratory (Durastop)	8.0 ± 2.3
Pilot (Edwards)	18.1 ± 4.3
Manufacturing (Stokes)	13.9 ± 8.5

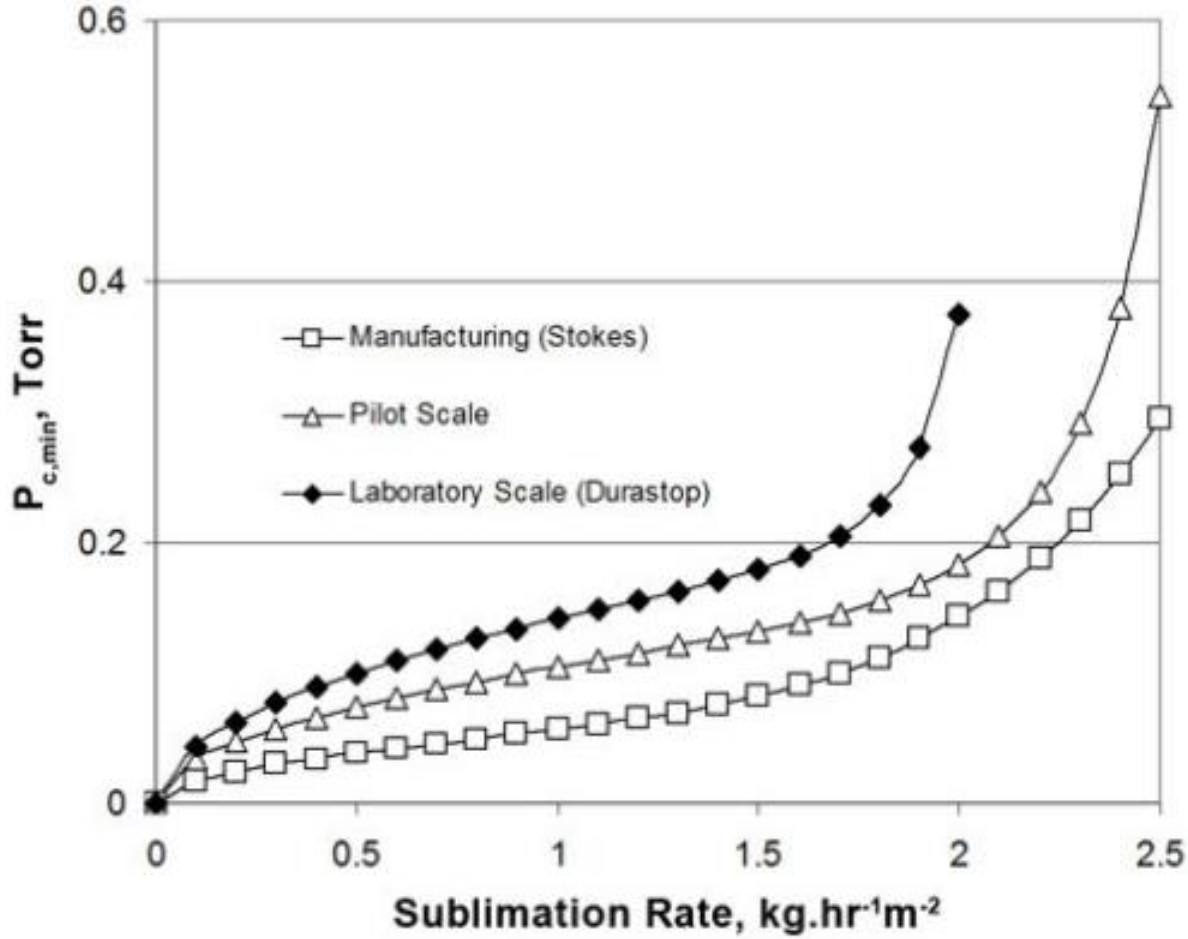
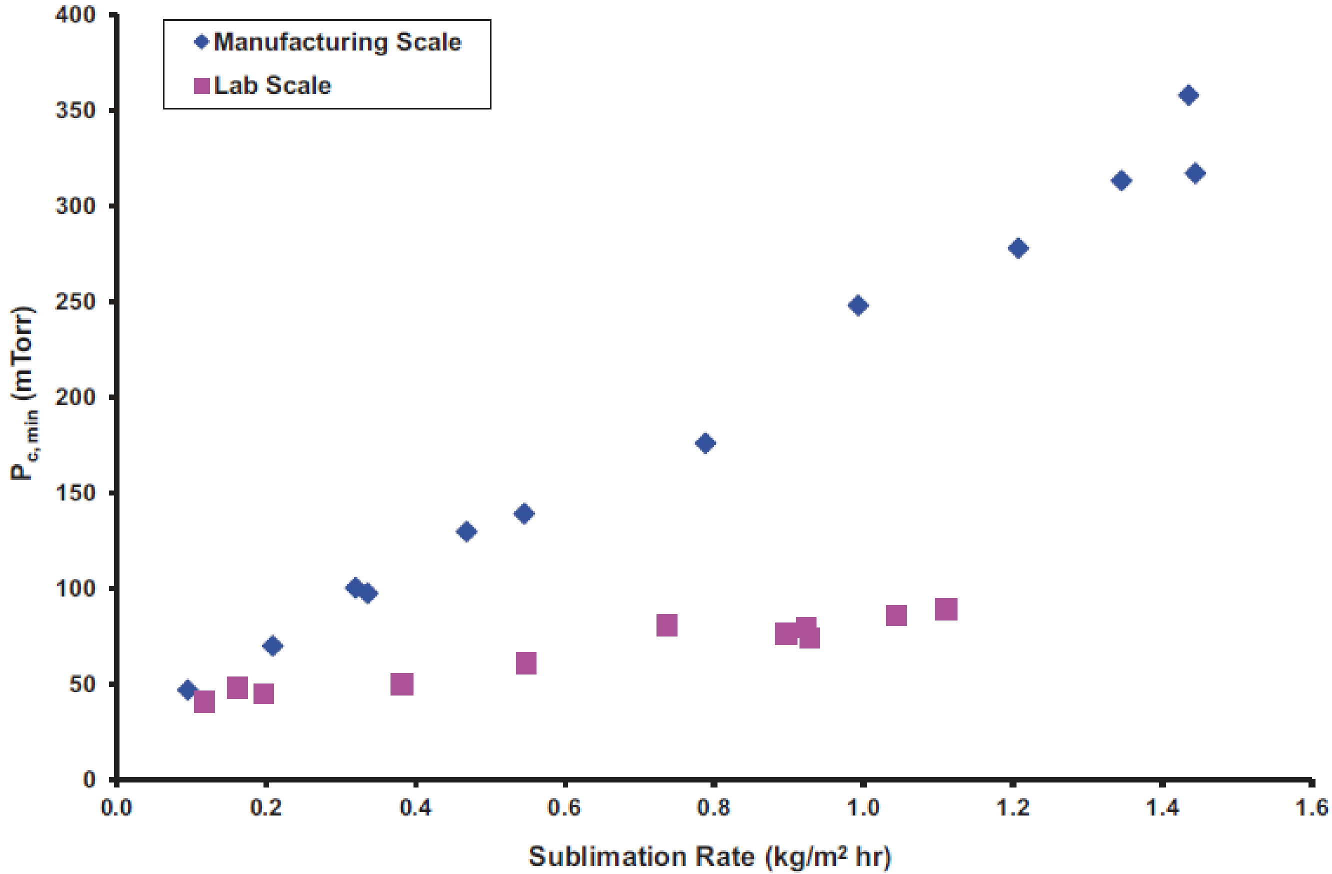


Figure 4. Comparison of minimum chamber pressure ($P_{c,min}$) as a function of sublimation rate.

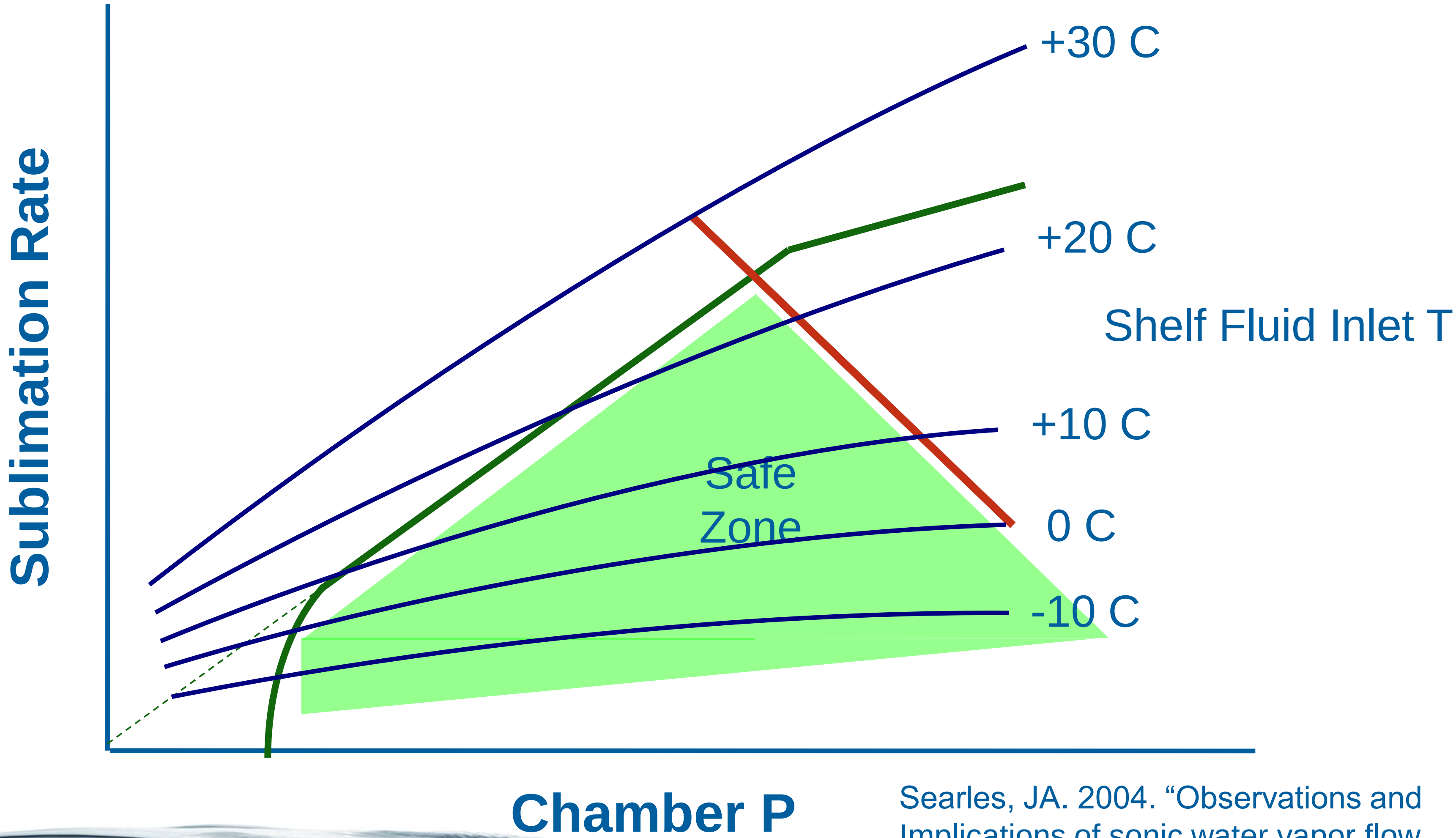
Rambhatla et al., AAPS PharmSciTech 2006; 7 (2) Article 39

Drying Rate Capability



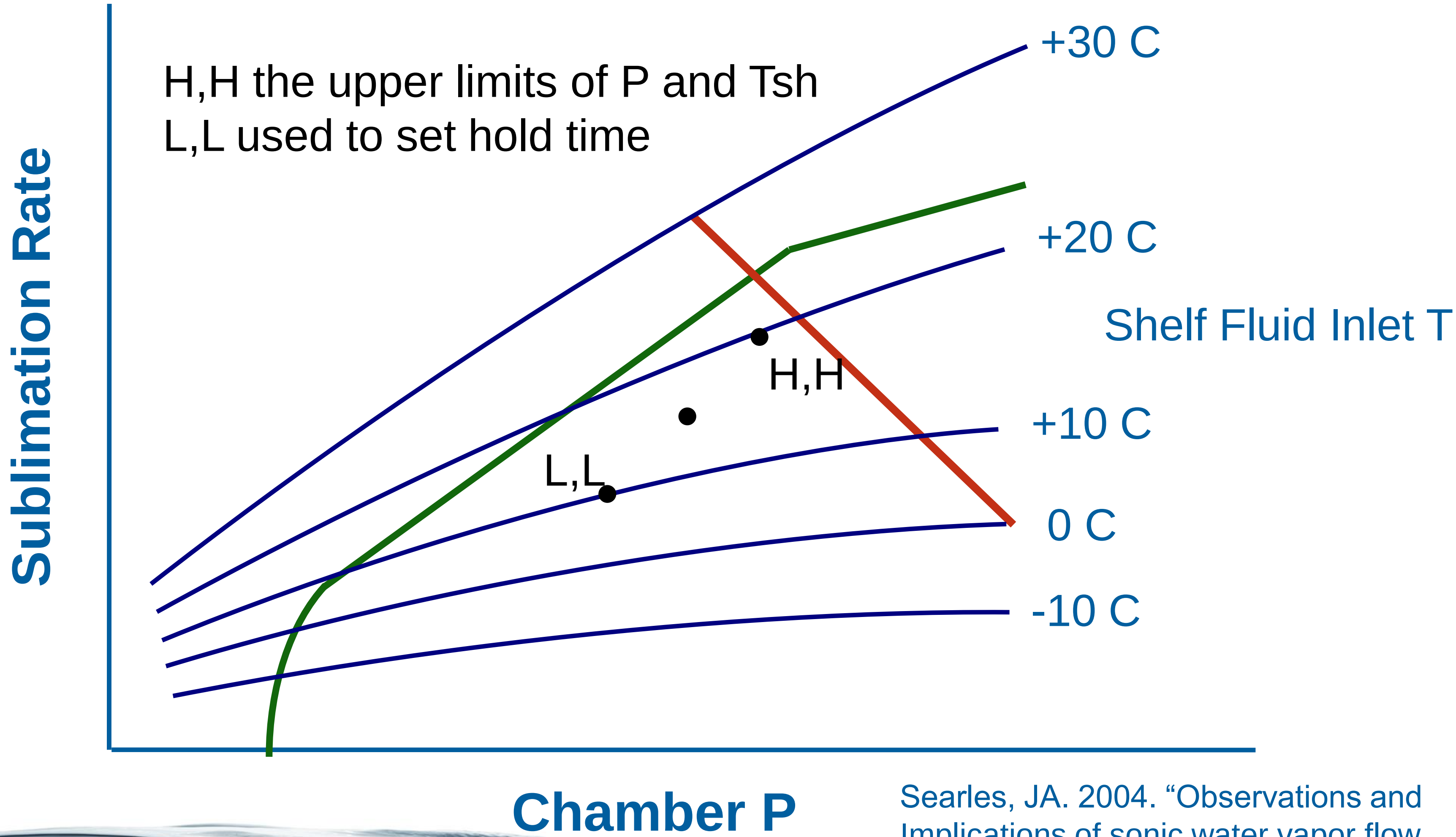
S. Patel et al. 2015. Chapter 14- Lyophilization Process Design and Development Using QbD Principles in F. Jameel et al. (eds.), Quality by Design for Biopharmaceutical Drug Product Development, AAPS Advances in the Pharmaceutical Sciences Series 18, DOI 10.1007/978-1-4939-2316-8_14

Cycle Design with Dryer Capability



Searles, JA. 2004. “Observations and Implications of sonic water vapor flow during freeze-drying” *American Pharm Review.* **7**(2) p. 58.

Cycle Design with Dryer Capability



Searles, JA. 2004. “Observations and Implications of sonic water vapor flow during freeze-drying” *American Pharm Review.* **7**(2) p. 58.

ONE 2 ONE™

Questions?

KNOWLEDGE | EXPERIENCE | EXPERTISE