Short Script: Theory 3 & Practical Work 1 - 3

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PDA EU Freeze – Drying in Practice

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Martin Christ
Osterode am Harz, Germany

Adapted from slides originally created by and with courtesy of PD Dr. Andrea Allmendinger

Shelf

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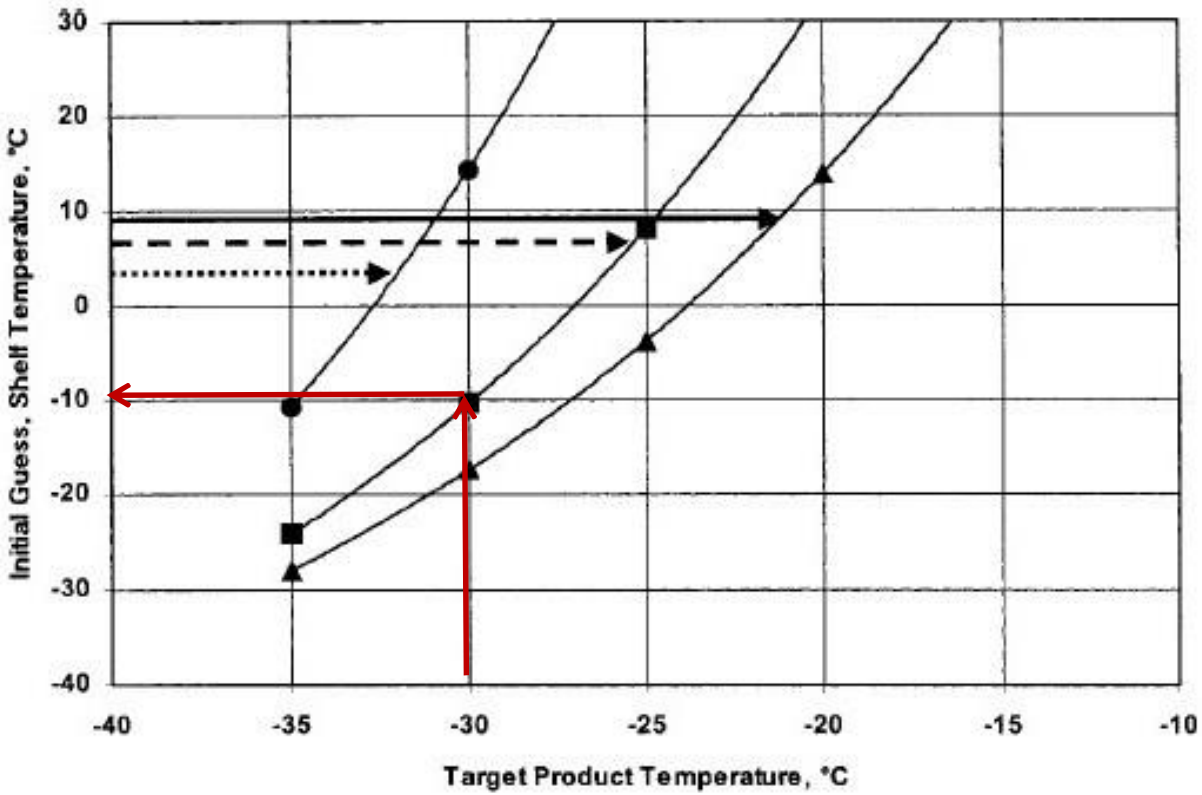
Review

Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice

Xiaolin (Charlie) Tang[1] and Michael J. Pikal[1,2]

total solid content: <1% 1-10% >10%



The total solid content defines the product resistance.

Initial shelf temperature estimation:

T_g' -27°C

↓

T(product target) below >2°C of T_g'

→ For instance -30°C

↓

Setting of T(shelf) depends on product resistance and thus on total solid content (sc)

↓

8%sc → -10°C

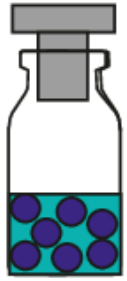
14%sc → -18°C

Literature recommendation: Figure reprinted from Tang X, Pikal MJ. Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice. Pharm Res. 2004;21(2):191–200. Copyright © 2004, Plenum Publishing Corporation

Chamber

Chamber pressure **>** Vapor pressure

500 mTorr



T_s = -30°C

Chamber pressure **<** Vapor pressure

100 mTorr

T_s = -30°C

- Vapor pressure of ice at -30°C → 380 µbar = 290 mTorr
- **Rule of thumb** for chamber pressure setpoint: 20-30% of vapor pressure at target product temperature
  For target T_p = -30°C → 26% * 380 µbar = ~100 mbar = 75 mTorr

- **Alternative:** $P_c = 0.29 \cdot 10^{(0.019 \cdot T_P)}$ For instance: P_c (Torr) = 0.29*10^(0.019*(-30))
  P_c = 0.078 Torr = 78 mTorr

Equation taken from: Tang X, Pikal MJ. Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice. Pharm Res. 2004;21(2):191–200.

Vapor Pressure of Ice

In contact with its own vapor

Temp	Vapor Pressure			Temp	Vapor Pressure		
°C	Pa	µmHg	µbar	°C	Pa	µmHg	µbar
0	611.1	4584.4	6111	-42	10.22	76.6	102
-2	517.7	3883.6	5177	-44	8.10	60.8	81
-4	437.4	3281.6	4374	-46	6.39	48.0	64
-6	368.7	2765.9	3687	-48	5.03	37.7	50
-8	309.9	2325.1	3099	-50	3.94	29.5	39
-10	259.9	1949.4	2599	-52	3.07	23.0	31
-12	217.3	1630.0	2173	-54	2.38	17.9	24
-14	181.2	1359.1	1812	-56	1.84	13.8	18
-16	150.6	1130.1	1506	-58	1.41	10.6	14
-18	124.9	936.9	1249	-60	1.08	8.1	11
-20	103.2	774.4	1032	-62	0.82	6.2	8.2
-22	85.07	638.2	851	-64	0.62	4.7	6.2
-24	69.88	524.3	699	-66	0.47	3.5	4.7
-26	57.23	429.3	572	-68	0.35	2.6	3.5
-28	46.71	350.4	467	-70	0.26	2.0	2.6
-30	38.00	285.1	380	-72	0.19	1.5	1.9
-32	30.81	231.1	308	-74	0.14	1.1	1.4
-34	24.89	186.7	249	-76	0.10	0.8	1.0
-36	20.03	150.3	200	-78	0.08	0.6	0.8
-38	16.07	120.5	161	-80	0.05	0.4	0.5
-40	12.84	96.3	128	-82	0.04	0.3	0.4

1 mbar = 750.1 microns 1 micron = 0.1333 Pa 1 Pa = 7.5006 microns

1 mbar = 100 Pa 1 micron = 0.0013 mbar 1 Pa = 0.01 mbar

mbar (cgs units) = millibar (10 E3 dyns/cm sq)

microns = micrometers of mercury

Pa (SI units) = Pascals (N/m^2)

micron = µmHg = mTorr

Lyophilization Program

working sheet Conservative

Regulation of vacuum: □Pirani □ MKS

Product assumptions: **T_g' = -32 °C;** drying safely **below** T_g'; **8%** solute conc.
Target T_p = -34 °C

Process step	Manual mode: Loading (Pre-cooling)	Freezing	Freezing	Freezing	Freezing	1° drying	1° drying	1° drying	2° drying	2° drying	Manual mode: stoopering
Time (hh:mm)		0:15	01:00	0:45						06:00	
Shelf temp. (°C)	20	5									
Vacuum (mbar)	off	off	off	off	off						750
Safety pressure (mbar)	off	off	off	off	off	0.26	0.26	0.26	0.26	0.26	
Δ T shelf (°C)		off	off	off	off	off	off	off	off	off	
Δ T product (°C)		off	off	off	off	off	off		off	off	
LyoControl Rx (%)		off	off	off	off	off	off	off	off	off	
camera interval (min)		15	60	1	5	10	10	10	10	60	

Lyophilization Program

working sheet Regular

Regulation of vacuum: □Pirani □ MKS

Product assumptions: **T_g' = -32°C**; drying **around** T_g'; **8%** solute conc.
Target T_p = -32 °C

Process step	Manual mode: Loading (Pre-cooling)	Freezing	Freezing	Freezing	Freezing	1° drying	1° drying	1° drying	2° drying	2° drying	Manual mode: stoopering
Time (hh:mm)		0:15	01:00	0:45						06:00	
Shelf temp. (°C)	20	5									
Vacuum (mbar)	off	off	off	off	off						750
Safety pressure (mbar)	off	off	off	off	off	0.26	0.26	0.26	0.26	0.26	
Δ T shelf (°C)		off	off	off	off	off	off	off	off	off	
Δ T product (°C)		off	off	off	off	off	off		off	off	
LyoControl Rx (%)		off	off	off	off	off	off	off	off	off	
camera interval (min)		15	60	1	5	10	10	10	10	60	

Lyophilization Program

working sheet Aggressive

Regulation of vacuum: □Pirani □ MKS

Product assumptions: **T_g' = -27°C**; drying **above** T_g'; **8%** solute conc.
Target T_p = -25 °C or -23 °C

Process step	Manual mode: Loading (Pre-cooling)	Freezing	Freezing	Freezing	Freezing	1° drying	1° drying	1° drying	2° drying	2° drying	Manual mode: stoopering
Time (hh:mm)		0:15	01:00	0:45						06:00	
Shelf temp. (°C)	20	5									
Vacuum (mbar)	off	off	off	off	off						750
Safety pressure (mbar)	off	off	off	off	off	0.26	0.26	0.26	0.26	0.26	
Δ T shelf (°C)		off	off	off	off	off	off	off	off	off	
Δ T product (°C)		off	off	off	off	off	off		off	off	
LyoControl Rx (%)		off	off	off	off	off	off	off	off	off	
camera interval (min)		15	60	1	5	10	10	10	10	60	

TO DO: Preparation

1. Compounding of formulations
   - Calculation of composition (seminar room)
   - Compounding (lab)
2. Filling
3. Stoppering
4. Freezing experiment with distilled water under vacuum to develop a general understanding of the critical temperature

Preparation

Materials:

- active ingredients and excipients (BSA, Sucrose, Mannitol, His, HisHCl-H2O, PS20)
- water for injection
- Schott bottles and beakers; measuring cylinder
- calculator
- scale, magnetic stirrer, spatula
- pH-meter
- pipettes

- 20 mL vials
- lyo stoppers

- thermo couples/ product sensors (2. day)

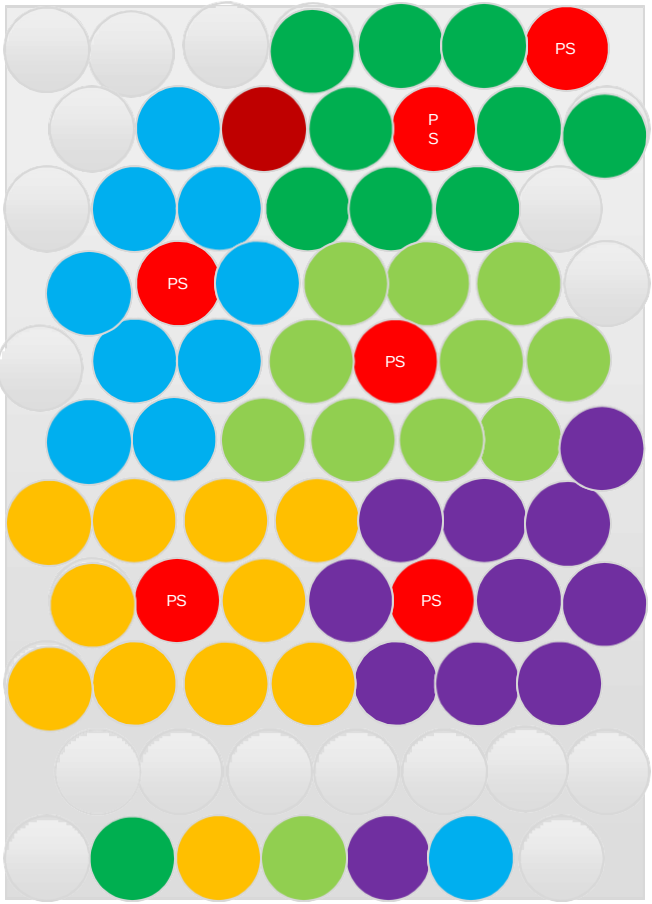
Preparation

Composition of formulations

#	Formulation	BSA	Excipient	Solid content (excipients)	Buffer system	Surfactant	T_g' / T_{eu}	Fill volume
1	Formulation 1	25 mg/mL	240 mM Sucrose	~80 mg/mL	20 mM HisHCl pH 6.0	0.02% (w/v) Polysorbat 20	~ -27	10 mL
2	Formulation 2/3	-	240 mM Sucrose	~80 mg/mL			~ -32	10 mL
3								5 mL
4	Formulation 4	-	120 mM Sucrose	~40 mg/mL			~ -32	10 mL
5	Formulation 5	-	220 mM Mannitol	~40 mg/mL			~-1	10 mL

Preparation - Loading

Proposal:



- **3** Lyophilizers / 3 groups
- One shelf (**77 vials**) will be fully loaded per group and lyophilizer
- Prepare your own loading scheme with different formulations including PAT sensors

1
2
3
4
5

Complete closed

PS Product sensor

Empty vial

Preparation

1. Calculate the volume needed per formulation depending on the loading scheme. Account for at least 20% overage.
2. Calculate the amount of excipients.
3. Calculate the amount of buffer needed.

As we are 3 groups – please consolidate and discuss who is preparing what and how much!

Preparation

working sheet

Composition of formulations:

Formulation #	Number of vials	Fill volume	Total volume needed	Total volume prepared* (L)	BSA concentration (mg/mL)	BSA (g)	Excipient concentration (mM)	Excipient concentration (g/L)	Excipient (mg)	Tensid + buffer system
1	_____	10 mL	_____	_____	25 mg/mL	_____	240 mM Sucrose	_____	_____	20 mM HisHCl pH 6.0: + 0.02% (w/v) PS20
2	_____	10 mL	_____	_____	-	-	240 mM Sucrose	_____	_____	
3		5 mL			-	-				
4	_____	10 mL	_____	_____	-	-	120 mM Sucrose	_____	_____	
5	_____	10 mL	_____	_____	-	-	220 mM Mannitol	_____	_____	
Total										_____ _____ _____

* Include 10% loss

Molar Mass:
Sucrose 342.3 g/mol
Mannitol 182.2 g/mol

Buffer receipt 1L:
- 2.196 g of His-HCl Monohydrat
- 1.477 g of Histidin, freie Base
- Ad 1 L with water

Preparation

1. Prepare the buffer and add the surfactant.
2. Compound the formulations by using the prepared buffer system
3. Fill the formulations into the glass vials and stopper them completely
4. Position the stoppers to allow for sublimation (semi-stoppered position)
5. Position the thermo couples
6. Load the lyophilizer
7. Program your recipe (Theory 3) and install/connect all PAT tools that you would like to use
8. Start the program and see the magic happen ☺