Theory 3

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PDA EU
Freeze – Drying in Practice

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

Theory 3

- Development of a lyophilization cycle
  - Which are the most important parameters?
  - How to choose them?
  - What happens if they are not chosen adequately?
- Finalization of cycles for practical work including choice of PAT tools

Development of a lyophilization cycle

1. Shelf temperature
   - 1°drying
   - 2°drying
2. Chamber pressure
3. Drying time (isothermal hold time)
4. Ramp time

Shelf temperature

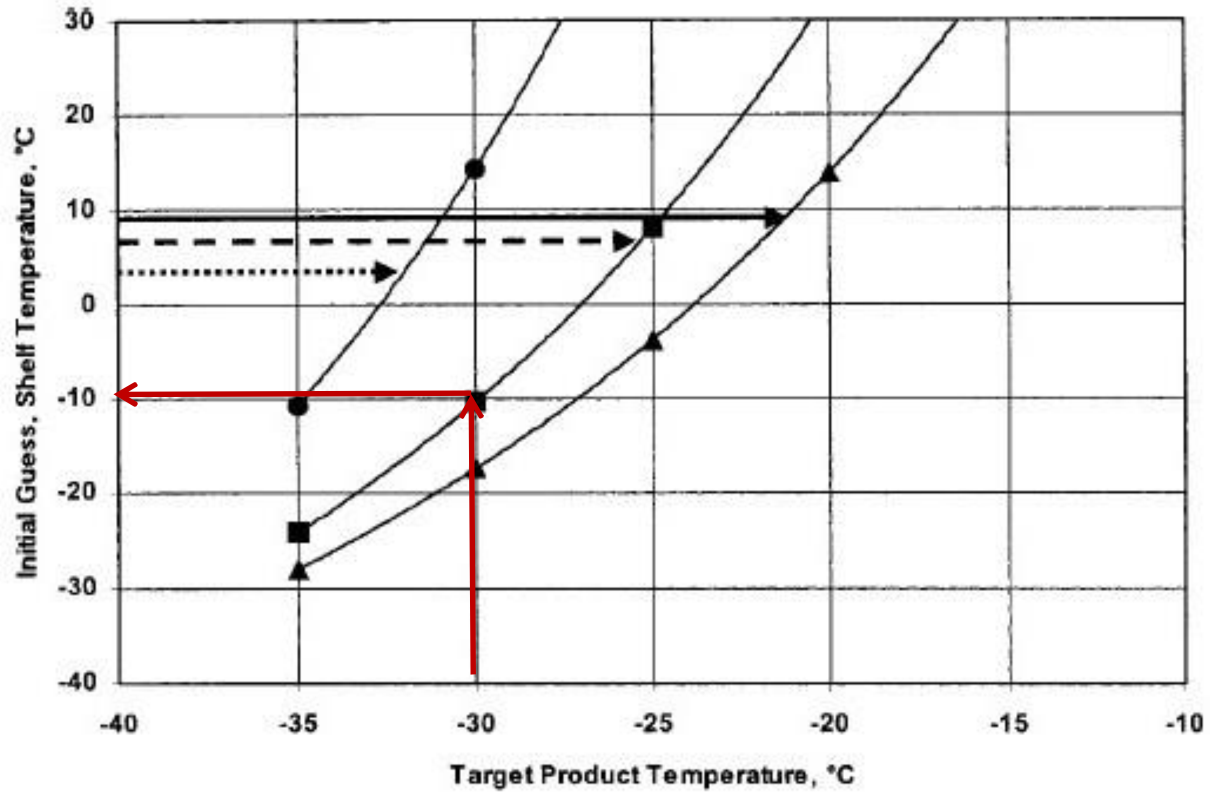
Pharmaceutical Research, Vol. 21, No. 2, February 2004 (© 2004)

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

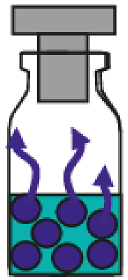
T(product target) below >2°C of T_g'
→ For instance -30°C

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.

Chamber pressure (P_c)

Chamber pressure **>** Vapor pressure	Chamber pressure **<** Vapor pressure
500 mTorr	100 mTorr
	
T_s = -30°C	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 °C	Vapor Pressure Pa	μmHg	μbar	Temp °C	Vapor Pressure 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

Development of a lyophilization cycle

1. Shelf temperature

   - 1°drying → T_g’ and T(collapse)

   - 2°drying → T_g!

2. Chamber vacuum

3. Drying time → product sensors, Pirani/MKS, pressure rise test

To keep in mind:

- T(product) needs to be kept lower than T_g’ and T(collapse)
- Practice: Different formulation have different Tg’ !

PAT

PAT	Epsilon 2-6D Lyo I	Epsilon 2-6D Lyo II	Epsilon2-4 Lyo III
Pirani	X	X	X
MKS	X	X	-
Comparative pressure measurement	X	X	-
PT100 (TC)	X	X	X
WTM+ (wireless TC)	X	X	X
LyoRx	X	X	X
Lyobalance	-	-	-
LyoCam	X	X	X
Controlled nucleation	X	-	-
Mass spectrometry	-	X	-
ΔP/Δt	X	X	-

End point detection

- **Time defined** cycles versus PAT
  - Δ T product (°C)
  - Δ T shelf (°C)
  - Comparative pressure measurement
  - Pressure rise test

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	03:30	0:01	0:18	49:00	3:55 (0.2K/min)	06:00	
Shelf temp. (°C)	20	5	5	-40	-40	-40	-22	-22	25	25	
Vacuum (mbar)	off	off	off	off	off	0.14	0.14	0.14	0.14	0.14	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)		0:25	01:00	0:35	03:30	0:01	0:25	30:00?**	03:20 (0.2 K/min)	06:00	
Shelf temp. (°C)	20	-5	-5*	-40	-40	-40	-15	-15	25	25	
Vacuum (mbar)	off	off	off	off	off	0.096 or 0.1 mbar	0.096 or 0.1 mbar	0.096 or 0.1 mbar	0.096 or 0.1 mbar	0.096 or 0.1 mbar	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	

*Controlled Nucleation after 1h hold time, hold time 15min, nuc at 7 mbar

**Comparative pressure measurement (10-15% difference)

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	03:30	0:15	00:60	15:00?*	00:05	06:00	
Shelf temp. (°C)	20	5	5	-40	-40	-40	20	20	25	25	
Vacuum (mbar)	off	off	off	off	off	0.14	0.14	0.14	0.14	0.14	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	

**Comparative pressure measurement (10-15% difference)

Aggressive Cycle: Single-step drying approach

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Lyophilization Process Design and Development: A Single-Step Drying Approach

Swapnil K. Pansare, Sajal M. Patel*

MedImmune, LLC, Dosage Form Design and Development Gaithersburg, Maryland 20878

- Tempting approach, but several limitations:
  - Comparably high protein conc. ≥ 50 g/L and moderate fill height feasible
  - More pronounced scale-up challenges: choked flow, condenser overload
  - Primary drying takes place in non-steady state during shelf ramping

Online calculators

- **SP Scientific LyoCalculator based on Pikal equations**
  - Not officially available anymore, but still can be accessed here

  http://web.archive.org/web/20200924004836/http:/www.spscientific.com/LyoCalc/Lyocalculator.html

- **LyoPRONTO**
  - Open source, theoretical assumptions in journal article
  - extended features (freezing calc, primary drying calc, design space calc, primary drying optimizer), but needs more advanced knowledge

  http://lyopronto.rcac.purdue.edu/