Theory 3

PDA EU
Freeze – Drying In Practice

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Adapted from slides originally created and kindly provided by 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

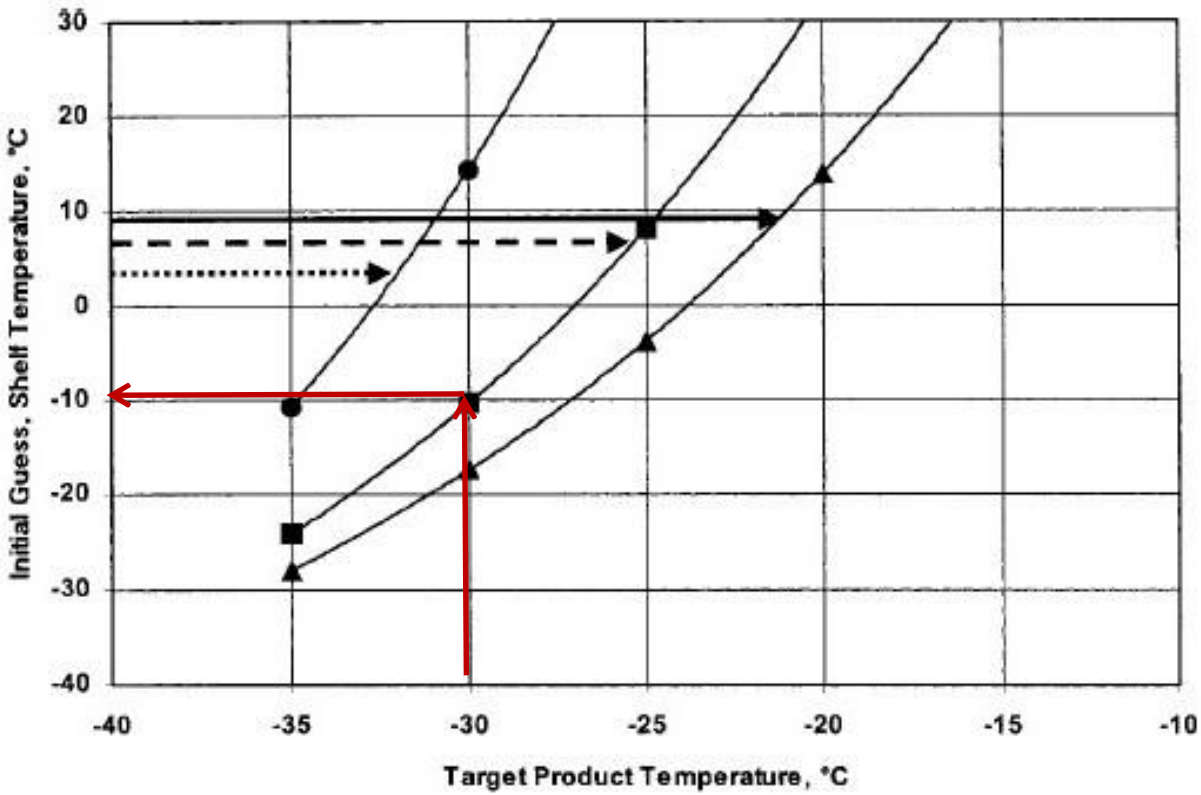
Pharmaceutical Research, Vol. 21, No. 2, February 2004 (© 2004)

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)

↓

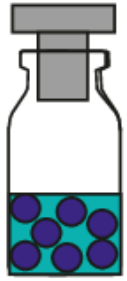
8%sc → -10°C
14%sc → -18°C

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. Copyright © 2004, Plenum Publishing Corporation

Chamber pressure (P_c)

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: Pc (Torr) = 0.29*10^(0.019*(-30))
  Pc = 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

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 below T_g‘; 8% solute conc.

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‘ = -27°C; drying below T_g‘; 8% solute conc.

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.

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	
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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	