Theory 2b

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PDA EU00144
Freeze-Drying in Practice
9 – 13 September 2024

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Theory 2b

- Basic principles of freeze drying processes
  - Physical understanding
  - Critical process parameters
- Development and composition of a (biological) formulation
- Development of a lyophilization cycle: Practical advice
  - How to approach it? What are the most important parameters?
  - How to choose them?
  - Development of cycles for practical work

Development of a lyophilization cycle: Practical advice

Where to find guidance?

- Pretty good starting point:

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]

https://doi.org/10.1023/B:PHAM.0000016234.73023.75

Pharmaceutical Research (2023) 40:2433–2455
https://doi.org/10.1007/s11095-023-03607-9

ORIGINAL RESEARCH ARTICLE

Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update

Serguei Tchessalov[1] · Vito Maglio[1] · Petr Kazarin[2] · Alina Alexeenko[2] · Bakul Bhatnagar[1] · Ekneet Sahni[3] · Evgenyi Shalaev[4]

- https://doi.org/10.1007/s11095-023-03607-9

How to approach it?

- Identify the maximum allowable/target product temperature during 1° drying
- Process design
  - Determine an adequate freezing procedure (annealing? Controlled nucleation?)
  - Ramps, equilibration steps, target freezing temperature, hold times
- 1°drying (simulation models or “paper-based”)
  - Determine combination of chamber pressure and shelf temperature
  - Ramp
  - Drying time (isothermal hold)
  - PAT for endpoint determination
- 2° drying
  - Ramp
  - Target shelf temperature and isothermal hold time

Freezing – advice for process design

- Decide if thermal treatment (annealing or controlled ice nucleation) shall be implemented → Theory 9
- Define loading temperature (usually: room temperature)
- Define process:
  - Equilibration step: decide temperature (above eq. freezing point) + hold time (min. 30min)
  - Coolin ramp rate (0.2 – 2 °C/min) → for scalability reasons: 0.3 – 0.7 °C/min
  - Target temperature: min. 5°C below Tg' (in most cases -40 to -45°C will do the job)
  - Hold time dependent on fill depth: ≤ 1cm: 1h, 1-2 cm: 2h, >2h: 4h

Based on: 1) "Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update." Tchessalov et al. Pharm Res 40, 2433–2455 (2023)., 2) "Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice". Tang, X., Pikal, M.J. Pharm Res 21, 191–200 (2004).

Primary Drying – advice for process design I

- Determine the **target product temperature** (T_p): amorphous formulations
  - For drying times >2d: $T_{collapse}$/$T_{eutectic}$ minus 2°C
  - For drying times <10h: $T_{collapse}$ minus 5°C
  - For drying times 10 ≤ t ≤ 2d: $T_{collapse}$ minus 3°C
  - Safety margin can also be calculated*
  - For (semi-)crystalline products: depending on equipment capabilities, a T_p of ~-10°C to -15°C is recommended (dependent on T_{eu} of the crystalline solute)
- Next, either use a simple heat/mass transfer model like 1) SP Scientific LyoCalculator or 2) LyoPRONTO or determine $\mathbf{p_{chamber}}$ and $\mathbf{T_{shelf}}$ „by hand“
- Ramp rate typically: 0.5 – 1 °C/min

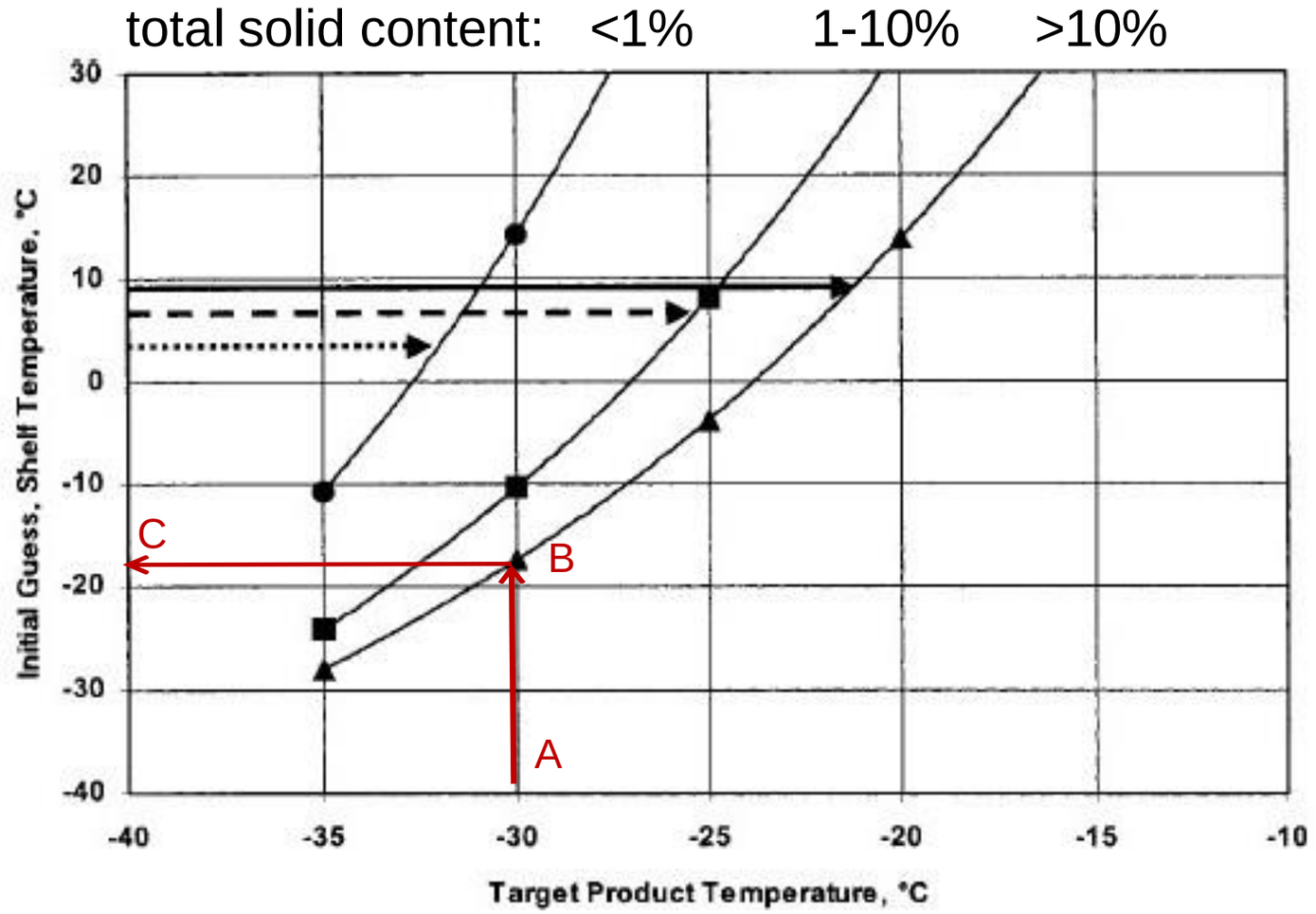
*”Impact of natural variations in freeze-drying parameters on product temperature history: application of quasi steady-state heat and mass transfer and simple statistics.” Pikal et al. AAPS PharmSciTech. 2018;19(7):2828–42.

Based on: 1) “Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update.” Tchessalov et al. Pharm Res 40, 2433–2455 (2023)., 2) “Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice”. Tang, X., Pikal, M.J. Pharm Res 21, 191–200 (2004).

Side note: Online calculators (heat/mass transfer simulations)

- **SP Scientific LyoCalculator (based on Pikal et al. model)**
  - Not officially available anymore, but still can be accessed here:
  - http://web.archive.org/web/20200924004836/http:/www.spscientific.com/LyoCalc/Lyocalculator.html
- **LyoPRONTO (Shivkumar et al.)**
  - Open source, theoretical assumptions in journal article
  - Tutorial available as book chapter
  - extended features like freezing calc, primary drying calc, design space calc, primary drying optimizer, but needs more advanced knowledge
  - Can be accessed here: https://lyopronto.geddes.rcac.purdue.edu/

Primary Drying – shelf temperature estimation



The total solid content defines the product resistance.

Initial shelf temperature estimation:
T_c = -27°C

T_p 2-3°C below of T_c
→ For instance T_p = -30°C [A]

Setting of T(shelf) depends on product resistance and thus on total solid content (sc); Example: 11% solid content [B]

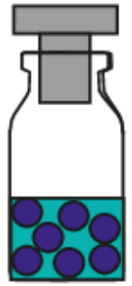
Readout is shelf temperature setpoint on y-axis: ~ -18 °C [C]

Reprinted from “Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice”. Tang, X., Pikal, M.J. Pharm Res 21, 191–200 (2004). Copyright [2004] © Springer Nature.

Primary Drying - Chamber pressure (p_c) estimation

Chamber pressure **>** Vapor pressure of ice at sublimation interface

p_c: 500 mTorr (0.67 mbar)



T_s = -30°C

Δp (chamber, ice) = driving force for sublimation!

Chamber pressure **<** Vapor pressure of ice at sublimation interface

p_c: 100 mTorr (0.13 mbar)

T_s = -30°C

- Vapor pressure of ice at -30°C → 0.31 mbar = 290 mTorr
- **Empiric equation:** $P_c = 0.29 \cdot 10^{(0.019 \cdot T_P)}$ p_c given in [Torr]; T_p = target product temp.
- For instance: **p_c** (Torr) = 0.29*10^(0.019*(-30)) = 0.078 Torr = **78 mTorr**

Vapor pressure of ice

Source: https://www.lyotechnology.com/assets/vpoi-chart-101915.pdf

Vapor Pressure of Ice

In contact with its own vapor

Temp °C	Vapor Pressure Pa	Vapor Pressure µmHg	Vapor Pressure µbar	Temp °C	Vapor Pressure Pa	Vapor Pressure µmHg	Vapor Pressure 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

Simulations (assuming: 20R vial, 10 mL fill, 11% total solid content, Tp=-30°C, amorphous)

Simulations for „by hand“ estimates:

User Inputs

Shelf Temperature	-18	[°C]
Chamber Pressure	0.104	[mBar]
Fill Volume	10	[mL]
Solute Concentration	11	[%]
Vial Outer Diameter	3.0	[cm]
Resistance Parameters R_o	2.3	
A_1	5.3	
A_2	0.7	

CLEAR VALUES | MATERIAL DATABASE | CALCULATE

Ts = -18 °C
p_c = 0.1 mbar

Report

Primary Drying Time	42.9	[Hrs]
Average Sublimation Rate per Vial	0.199	[g/Hr]
Maximum Product Temperature	-30.7	[°C]

CALCULATE | DETAILED OUTPUT | DOWNLOAD DATA AS CSV

Simulations optimizing for T_p = -30°C:

User Inputs

Shelf Temperature	-14	[°C]
Chamber Pressure	0.07	[mBar]
Fill Volume	10	[mL]
Solute Concentration	11	[%]
Vial Outer Diameter	3.0	[cm]
Resistance Parameters R_o	2.3	
A_1	5.3	
A_2	0.7	

CLEAR VALUES | MATERIAL DATABASE | CALCULATE

Ts = -14 °C
p_c = 0.07 mbar

Report

Primary Drying Time	34.4	[Hrs]
Average Sublimation Rate per Vial	0.249	[g/Hr]
Maximum Product Temperature	-29.9	[°C]

DETAILED OUTPUT | DOWNLOAD DATA AS CSV

Material Database

	Materials	R_o	A_1	A_2
USE	Povidone, 5% (v/v)	1.1	5	0
USE	Sucrose, 5% (w/w) with ice nucleated at -5°C	1	2.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -10°C	1.5	3.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -15°C (note: values were extrapolated)	2.3	5.3	0.7

Calculations performed with SP Scientific LyoCalculator

Secondary drying – advice for process design

- Define ramp and target shelf temperature; p_c not too important*
- Ramp is critical for preventing collapse (amorphous products)
  - 0.1 to 0.2 °C/min amorphous
  - 0.3 to 0.4 °C/min (semi-)crystalline
- Define isothermal hold at target shelf temperature
  - Often, 3-6h at 40-50 °C suffice to reach < 0.5% (w/w) RMC (see theory 2a, slide 19 for sucrose 5-15%)

* Pc has almost no impact on drying rate, if kept below 0.267 mbar; for further details refer to: "The secondary drying stage of freeze drying: drying kinetics as a function of temperature and chamber pressure". Pikal et al. Int. J. Pharm. 60:3 (1990),

- Based on: 1) "Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update." Tchessalov et al. Pharm Res 40, 2433–2455 (2023)., 2) "Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice". Tang, X., Pikal, M.J. Pharm Res 21, 191–200 (2004).

Development of cycles for practical work

Experimental overview

- 3 different lab freeze dryers are available for runs
- Five different model formulations will be prepared and freeze dried:

Composition of formulations

#	Formulation	BSA	Excipient	Solid content	Buffer system	Surfactant	T_g' / T_{eu}	Fill volume
1	Formulation 1	25 mg/mL	240 mM Sucrose	~105 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

- Suggestion: run three differently conservative/aggressive cycles to observe different process behaviors and product appearance

Available freeze dryer equipment

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	X X	-
PT100 (TC)			
WTM+ (wireless TC)	X	X	X
LyoRx	X	X	X
LyoCam	X	X	X
Controlled nucleation	X	-	-
Mass spectrometry	-	X	-
$\Delta T_p/\Delta T_s$	X	X	-

working sheet
Conservative

Lyophilization Program

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

Regulation of vacuum: x Pirani □ MKS 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	02:00	00:01	00:20	52:00	05:50	02:00	
Shelf temp. (°C)	20	5	5	-40	-40	-40	-20	-20	50	50	
Vacuum (mbar)	off	off	off	off	off	0.12	0.12	0.12	0.12	0.12	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	

Conservative Cycle

Material Database

	Materials	R_o	A_1	A_2
USE	Povidone, 5% (v/v)	1.1	5	0
USE	Sucrose, 5% (w/w) with ice nucleated at -5°C	1	2.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -10°C	1.5	3.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -15°C (note: values were extrapolated)	2.3	5.3	0.7

User Inputs

?	Shelf Temperature	-20	[°C]
?	Chamber Pressure	0.07	[mBar]
?	Fill Volume	10	[mL]
?	Solute Concentration	8	[%]
?	Vial Outer Diameter	3.0	[cm]
?	Resistance Parameters R_o	1.5	
	A_1	3.4	
	A_2	0.7	

CLEAR VALUES | MATERIAL DATABASE | CALCULATE

Report

?	Primary Drying Time	40.9	[Hrs]
?	Average Sublimation Rate per Vial	0.218	[g/Hr]
?	Maximum Product Temperature	-34.0	[°C]

CALCULATE | DETAILED OUTPUT | DOWNLOAD DATA AS CSV

<u>Calculated „by hand“:</u>

- T_s = -21 °C
- Pc = ~66 mTorr = 88 µbar

working sheet
Regular

Lyophilization Program

Product assumptions: **T_c = -30°C**; drying **around/slightly above** T_c; **8%** solute conc.; Target T_p = -30 °C

Regulation of vacuum: □Pirani x MKS

Implement Annealing?
T_s = -15°C
3h hold

Additional time:
25+180+25 +120
= 5h 50m

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	02:00	00:01	00:26	32:00	05:20	02:00	
Shelf temp. (°C)	20	5	5	-40	-40	-40	-14	-14	50	50	
Vacuum (mbar)	off	off	off	off	off	0.07	0.07	0.07	0.07	0.07	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	

Regular Cycle

Material Database

	Materials	R_o	A_1	A_2
USE	Povidone, 5% (v/v)	1.1	5	0
USE	Sucrose, 5% (w/w) with ice nucleated at -5°C	1	2.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -10°C	1.5	3.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -15°C (note: values were extrapolated)	2.3	5.3	0.7

User Inputs

?	Shelf Temperature	-14	[°C]
?	Chamber Pressure	0.07	[mBar]
?	Fill Volume	10	[mL]
?	Solute Concentration	8	[%]
?	Vial Outer Diameter	3.0	[cm]
?	Resistance Parameters R_o	2.3	
	A_1	5.3	
	A_2	0.7	

CLEAR VALUES | MATERIAL DATABASE

CALCULATE

Report

?	Primary Drying Time	35.9	[Hrs]
?	Average Sublimation Rate per Vial	0.248	[g/Hr]
?	Maximum Product Temperature	-29.9	[°C]

CALCULATE | DETAILED OUTPUT | DOWNLOAD DATA AS CSV

Calculated „by hand“:

- T_s = -10 to -15 °C
- Pc = ~78 mTorr = 104 µbar

working sheet
Aggressive

Lyophilization Program

Product assumptions: **T_g' = -27°C**; drying **above** T_g'; **10.5%** solute conc.
Target T_p = -25 to -26°C

Regulation of vacuum: □Pirani x MKS

Implement **CN** here? LyoCalc w/ -5° Suc

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	02:00	00:01	01:05	12:00	02:05	02:00	
Shelf temp. (°C)	20	5	5	-40	-40	-40	25	25	50	50	
Vacuum (mbar)	off	off	off	off	off	0.15	0.15	0.15	0.15	0.15	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	

Aggressive Cycle

Material Database

	Materials	R_o	A_1	A_2
USE	Povidone, 5% (v/v)	1.1	5	0
USE	Sucrose, 5% (w/w) with ice nucleated at -5°C	1	2.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -10°C	1.5	3.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -15°C (note: values were extrapolated)	2.3	5.3	0.7

User Inputs

?	Shelf Temperature	25	[°C]
?	Chamber Pressure	0.15	[mBar]
?	Fill Volume	10	[mL]
?	Solute Concentration	10.5	[%]
?	Vial Outer Diameter	3.0	[cm]
?	Resistance Parameters R_o	1	
	A_1	2.4	
	A_2	0.7	

CLEAR VALUES | MATERIAL DATABASE | CALCULATE

Report

?	Primary Drying Time	11.6	[Hrs]
?	Average Sublimation Rate per Vial	0.748	[g/Hr]
?	Maximum Product Temperature	-25.6	[°C]

CALCULATE | DETAILED OUTPUT | DOWNLOAD DATA AS CSV

Calculated „by hand“:

- T_s = ~ -4°C
- Pc = ~97 mTorr = 129 µbar