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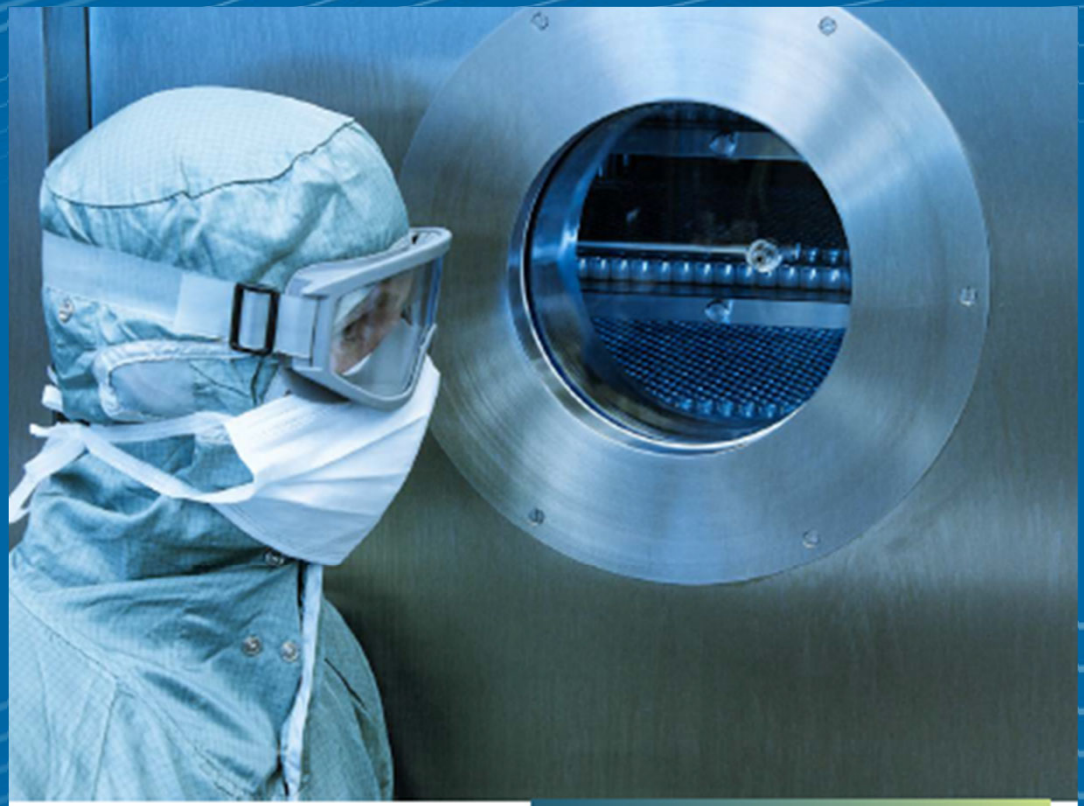
Theory 3



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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?
- Simulation tools
- 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 vacuum
3. Drying time

Shelf temp.

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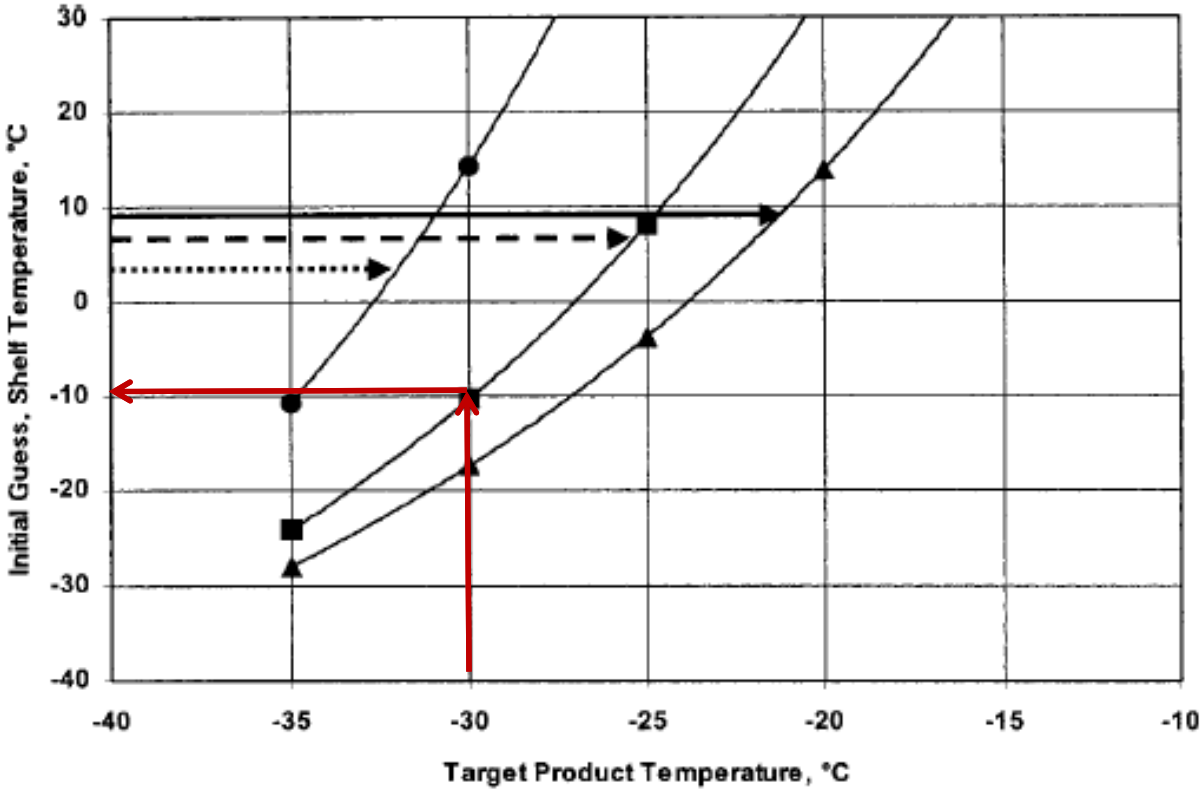
Review

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.

Tg' -27°C

↓

T(product) <2°C of Tg'
→ z.B. -30°C

↓

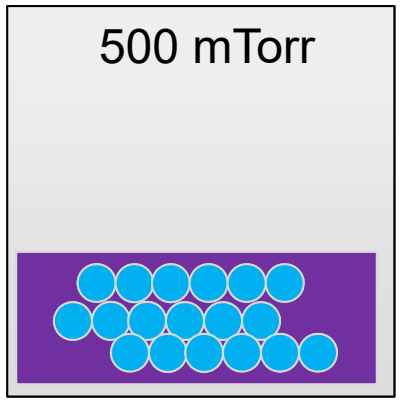
Setting of T(shelf) depends on product resistance and thus on total solid content (sc)

↓

4%sc → +5°C
8%sc → -10°C

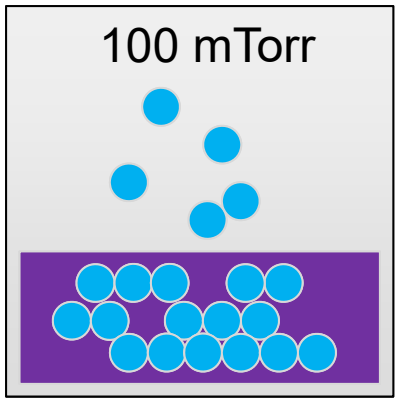
Chamber vacuum

Chamber vacuum > Vapor pressure



-30 ° C

Chamber vacuum < Vapor pressure



-30 ° C

- Vapor pressure of ice at -30 ° C → 380 µbar = 290 mTorr
- Chamber pressure: 20-30% vapor pressure at defined product temperature → ~100mbar = 75mTorr

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)

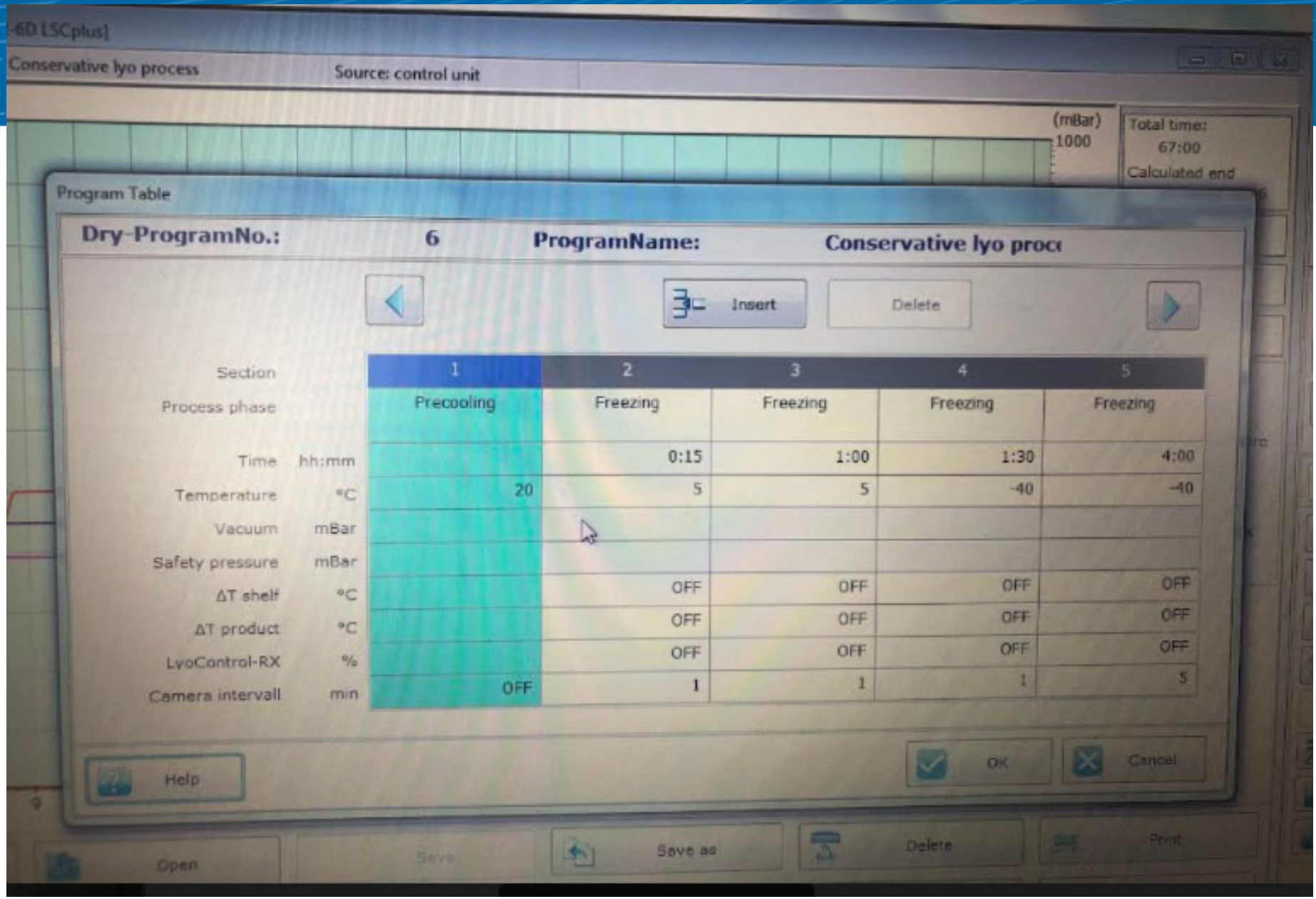
micron = µmHg = mTorr

Demonstration of lyo simulation tool

Development of a lyophilization cycle

1. Shelf temperature
    - 1 ° drying → Tg' and T(collapse)
    - 2 ° drying → Tg!
2. Chamber vacuum
3. Drying time → produkt sensors, Pirani/MKS, pressure rise test

To keep in mind:
- T(product) needs to be higher than Tg' and T(collapse)
- Practice: Different formulation have different Tg' !


-6D LSCplus]
Conservative lyo process
Source: control unit
(mBar)
1000
Total time:
67:00
Calculated end
Program Table
Dry-ProgramNo.: 6
ProgramName: Conservative lyo proc
Insert
Delete
Section
Process phase
1
Precooling
2
Freezing
3
Freezing
4
Freezing
5
Freezing
Time hh:mm
0:15
1:00
1:30
4:00
Temperature °C
20
5
5
-40
-40
Vacuum mBar
Safety pressure mBar
ΔT shelf °C
OFF
OFF
OFF
OFF
ΔT product °C
OFF
OFF
OFF
OFF
LyoControl-RX %
OFF
OFF
OFF
OFF
Camera intervall min
OFF
1
1
1
5
Help
OK
Cancel
Open
Save
Save as
Delete
Print

Recipes

	Lyo 1	Lyo 2	Lyo 3
Lyo cycle	normal	aggressive	conservative
Manual mode: Loading	20°C		
Cooling and Equilibration	5°C, 1h		
Freezing	0.5 K/min		
Equilibration	-40°C, 4 h		
Ramp to 1° drying	0.33 K/min		
1° drying	-10°C, 100 mTorr	20°C 100 mTorr	-20°C 100 mTorr
End point 1° drying	50 h Time defined! (ΔTP<3°C optional)	50 h Time defined (ΔTP<3°C optional)	50 h Time defined
Ramp to 2° drying	0.2 K/min		
2° drying	20°C, 6 h	35°C, 6 h	20°C, 6 h
Manual mode: end point	5°C		
partial vacuum, stoppering	750 mbar		

Controlled nucleation:
- Nucl. Temp -5 ° C
- 7mbar

PAT

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

End point detection

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

Lyophilization Program

working sheet

Regulation of vacuum: ☐Pirani ☐ MKS

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	01:30						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	