

# Theory 3

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## Freeze Drying in Practice



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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?
- 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



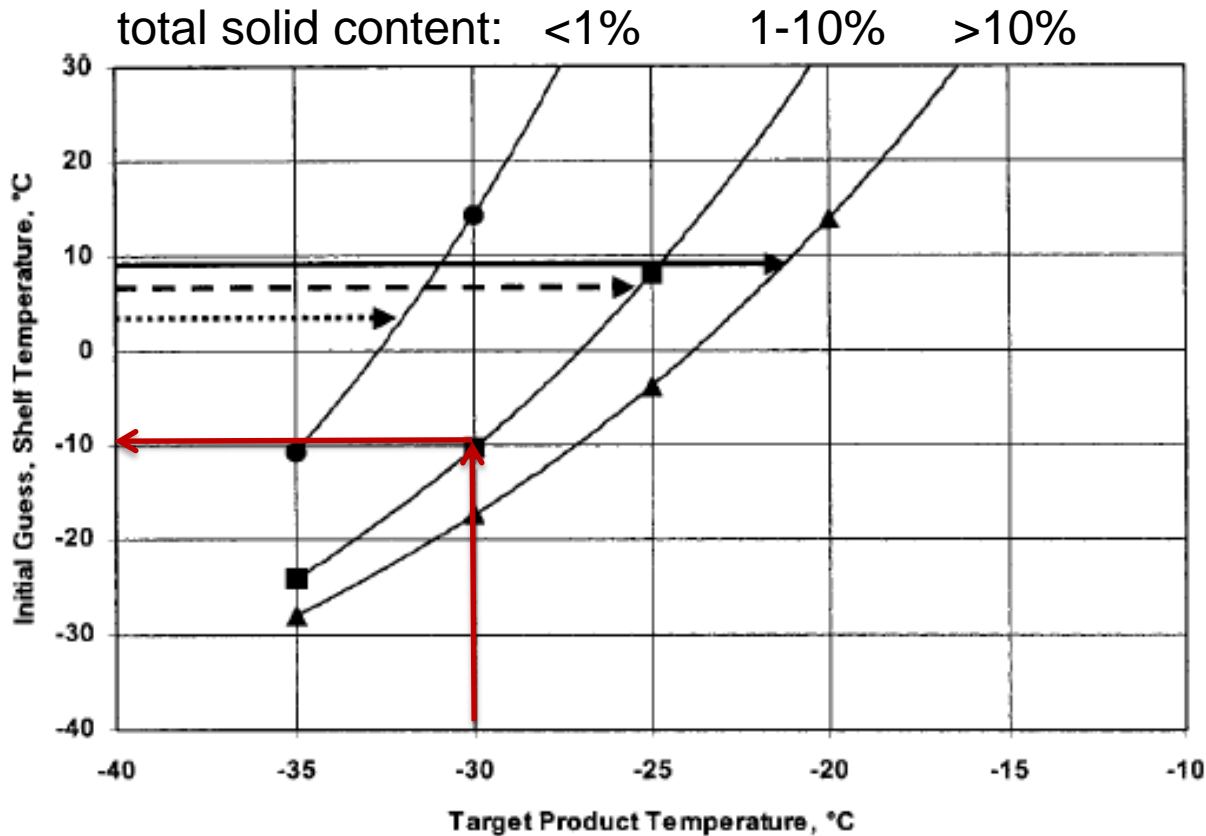
# Shelf temp.

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

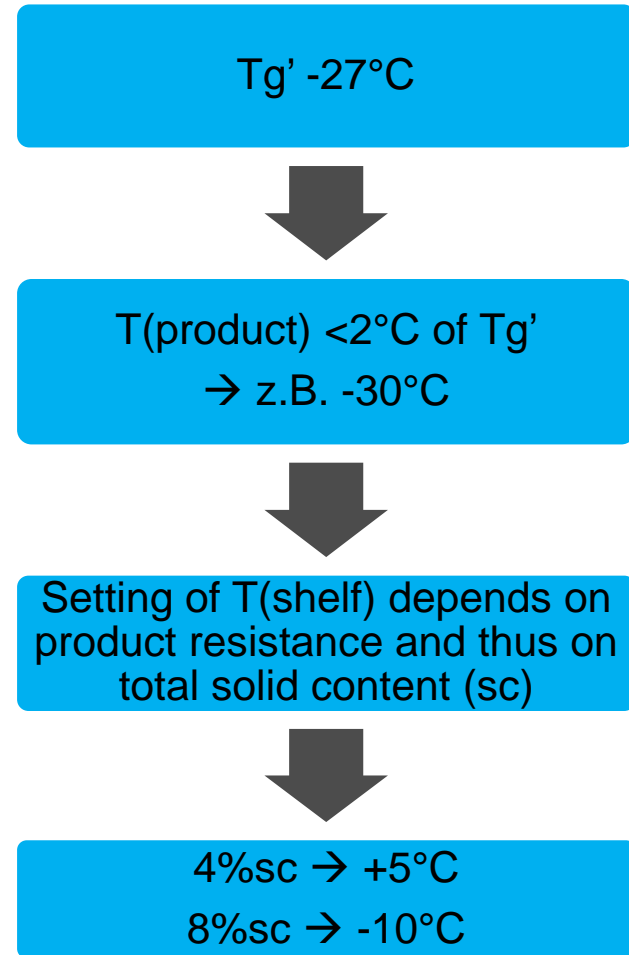
Review

## Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice

Xiaolin (Charlie) Tang<sup>1</sup> and Michael J. Pikal<sup>1,2</sup>



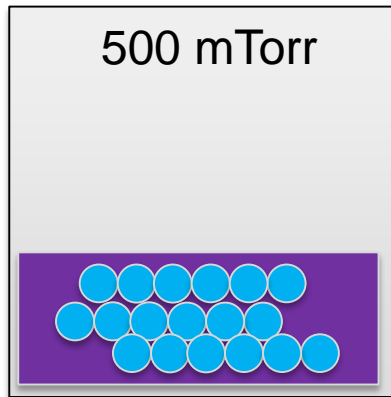
The total solid content defines the product resistance.





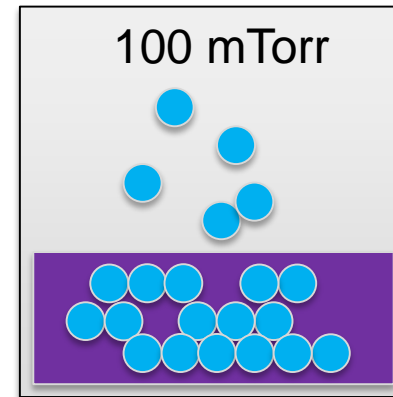
# Chamber vacuum

Chamber vacuum > Vapor pressure



-30° C

Chamber vacuum < Vapor pressure



-30° C

- Vapor pressure of ice at -30° C → 380  $\mu$ bar = 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 °C	Vapor Pressure			Temp °C	Vapor Pressure		
	Pa	µmHg	µbar		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<sup>2</sup>)

micron = µmHg = mTorr



# 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' !



Program Table

Dry-ProgramNo.:

6

ProgramName:

Conservative lyo proc



Insert

Delete



Section		1	2	3	4	5
Process phase		Precooling	Freezing	Freezing	Freezing	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	Controlled nucleation: • Nucl. Temp -5° C • 7mbar	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! ( $\Delta T P < 3^{\circ} C$ optional)	50 h Time defined ( $\Delta T P < 3^{\circ} C$ 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		



# PAT

PAT	Epsilon 2-6	Epsilon 2-6	Epsilon2-4
	Lyo I <i>(controlled nucleation)</i>	Lyo II	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
$\Delta P/\Delta t$			



# End point detection

- **Time defined** cycles versus PAT
  - $\Delta T$  product ( $^{\circ}$  C)
  - $\Delta T$  shelf ( $^{\circ}$  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	