PDA
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Theory 3

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- 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

Development of a lyophilization cycle

1. Shelf temperature
    - 1 ° drying
    - 2 ° drying
2. Chamber vacuum
3. Drying time

Shelf temp.

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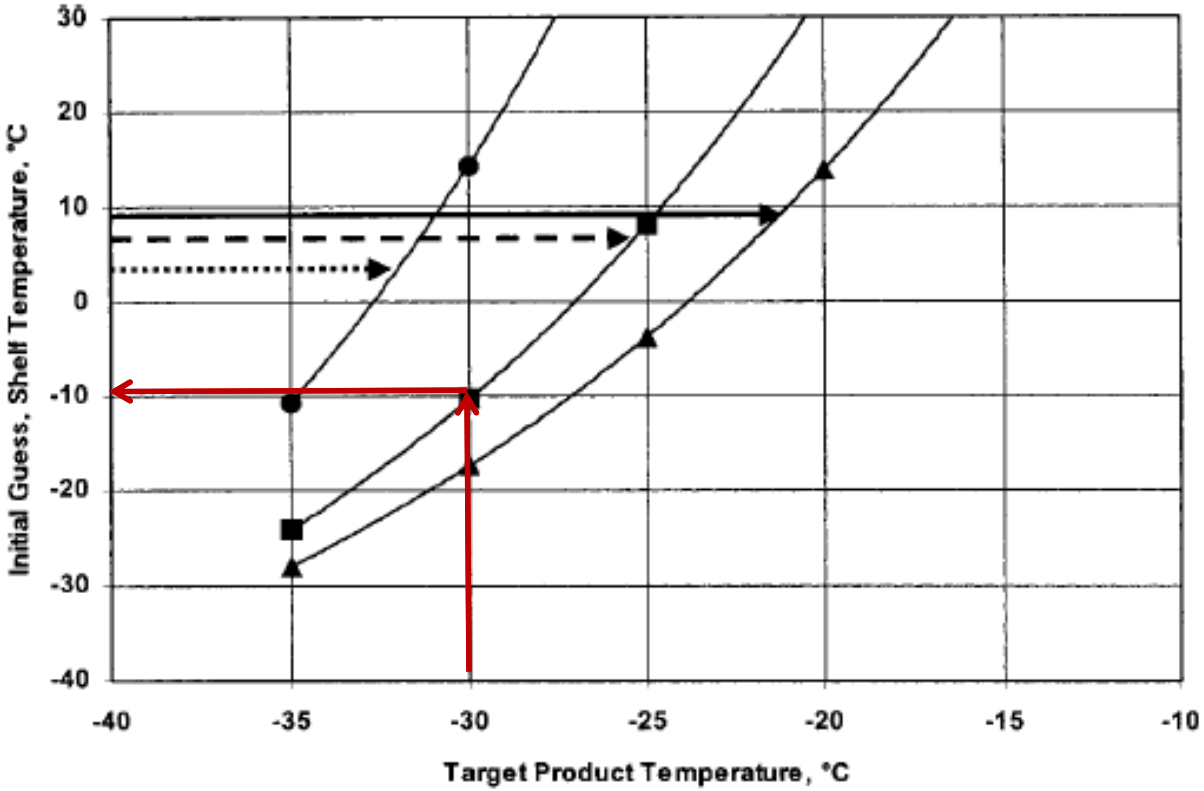
Review

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

↓

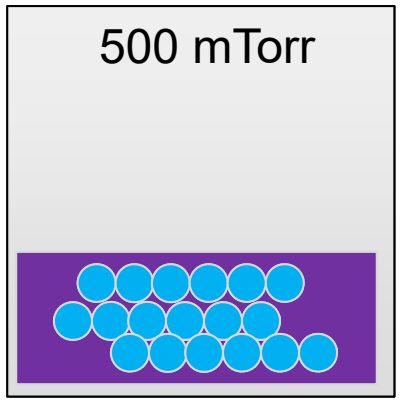
Setting of T(shelf) depends on product resistance and thus on total solid content (sc)

↓

4%sc → +5°C
8%sc → -10°C

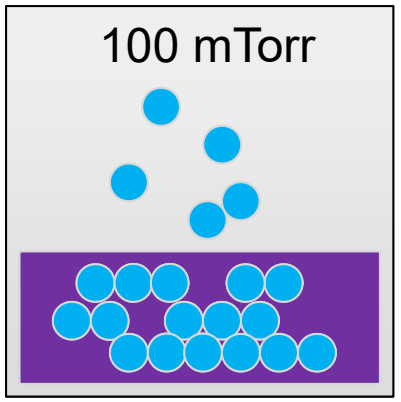
Chamber vacuum

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

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' !

Demonstration of lyo simulation tool

Lyophilization Program

working sheet

Regulation of vacuum: _____

Process step	Time	Shelf temp. (°C)	Vacuum (mbar)	Safety pressure	Δ T shelf (°C)	Δ T product (°C)	LyoControl Rx (%)	camera interval (min)
Manual (loading)		20						
Freezing					off		off	
Freezing					off		off	
Freezing					off		off	
1° drying					off		off	
1° drying					off		off	
1° drying					off		off	
2° drying					off		off	
2° drying					off		off	
Manual steps: end temp., part. vacuum, stoppering		5	750					