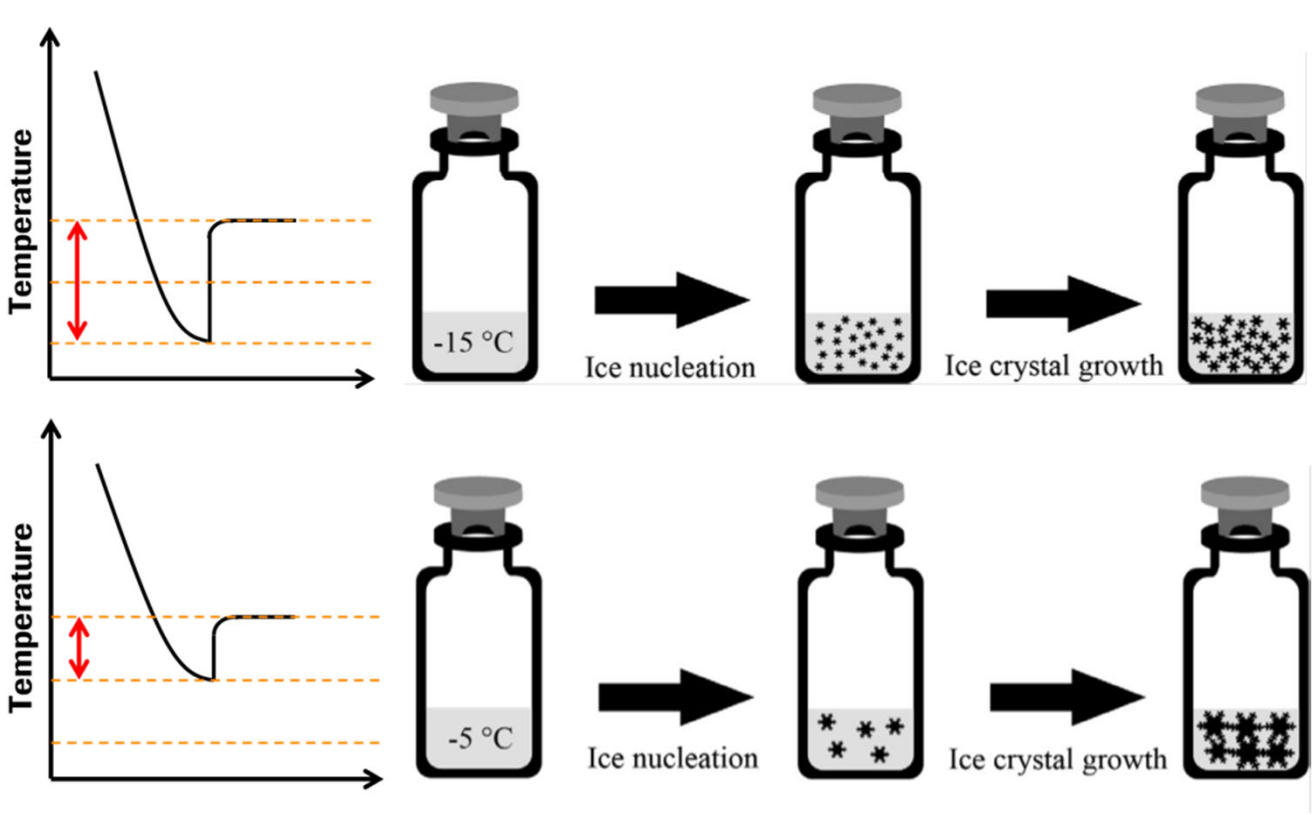
Progress of drying

Controlled nucleation



Low degree of supercooling

↓

Big dentritic ice crystals

↓

Morphology

↓

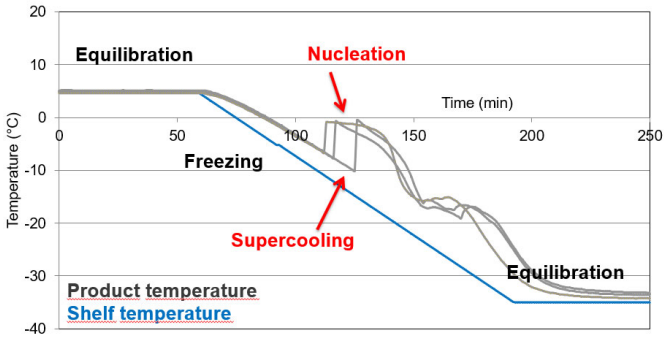
Drying time

- Increases inter-/intra-batch- and vial-to-vial homogeneity
- Shorter primary drying
- Better stability (?)

Review: Geidobler R, Winter G. Eur J Pharm Biopharm. 2013 Oct;85(2):214-22

Methods for controlled nucleation

Praxair.mp4



Vacuum induced surface freezing

(Kramer et al., SynchroFreeze)

Ice fog technique

Altenratives: annealing

Rapid depressurization

(ControLyo/ LyoCon)

Ultrasound induced freezing

Review: Geidobler R, Winter G.

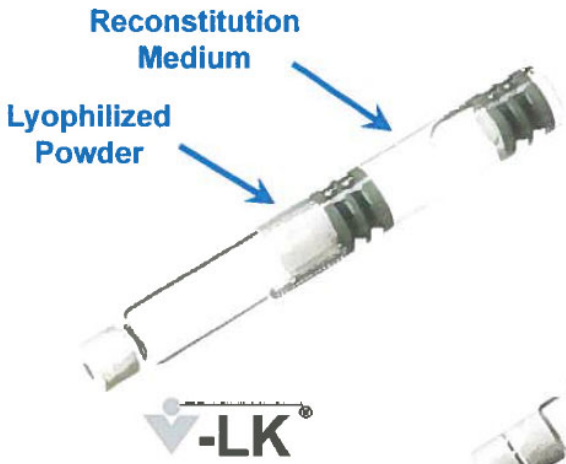
Eur J Pharm Biopharm. 2013

Oct;85(2):214-22.

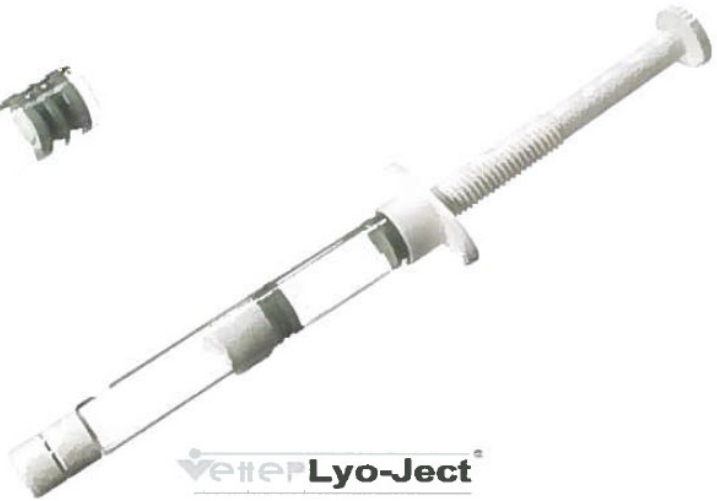
Primary packaging

Vial

(different coatings)



Cartridge



Syringe

(Dual chamber syringe)

Solid state characterization

1. Cake appearance – visual inspection
2. Cake/ pore structure:
   - Polymer embedding
   - Scanning electron microscopy
3. Specific surface area (BET)
4. Xray powder diffraction (cristallinity/amorphous structures)
5. Residual moisture (e.g. Karl-Fischer)
6. Reconstitution time

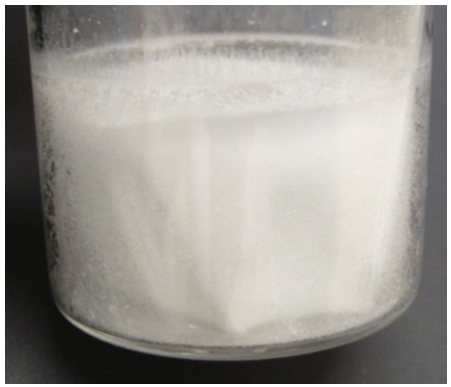
Watch out for Theory 9 !!

Visual inspection

Patel et al: Lyophilized Drug Product Cake Appearance: What Is Acceptable?
Patel S, Nail S, Pikal M, Geidobler R, Winter G, Hawe A, Davagnino J, Rambhatla Gupta S.
J Pharm Sci. 2017 Jul;106(7):1706-1721. doi: 10.1016/j.xphs.2017.03.014.

Cosmetic defects versus impact on product quality?

Intact cake



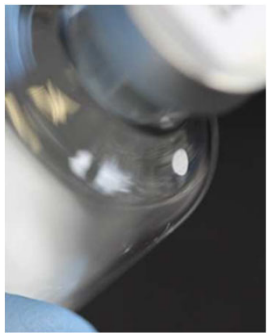
light collapse/melt-back

severe collapse/melt-back

complete collapse/melt-back

crack

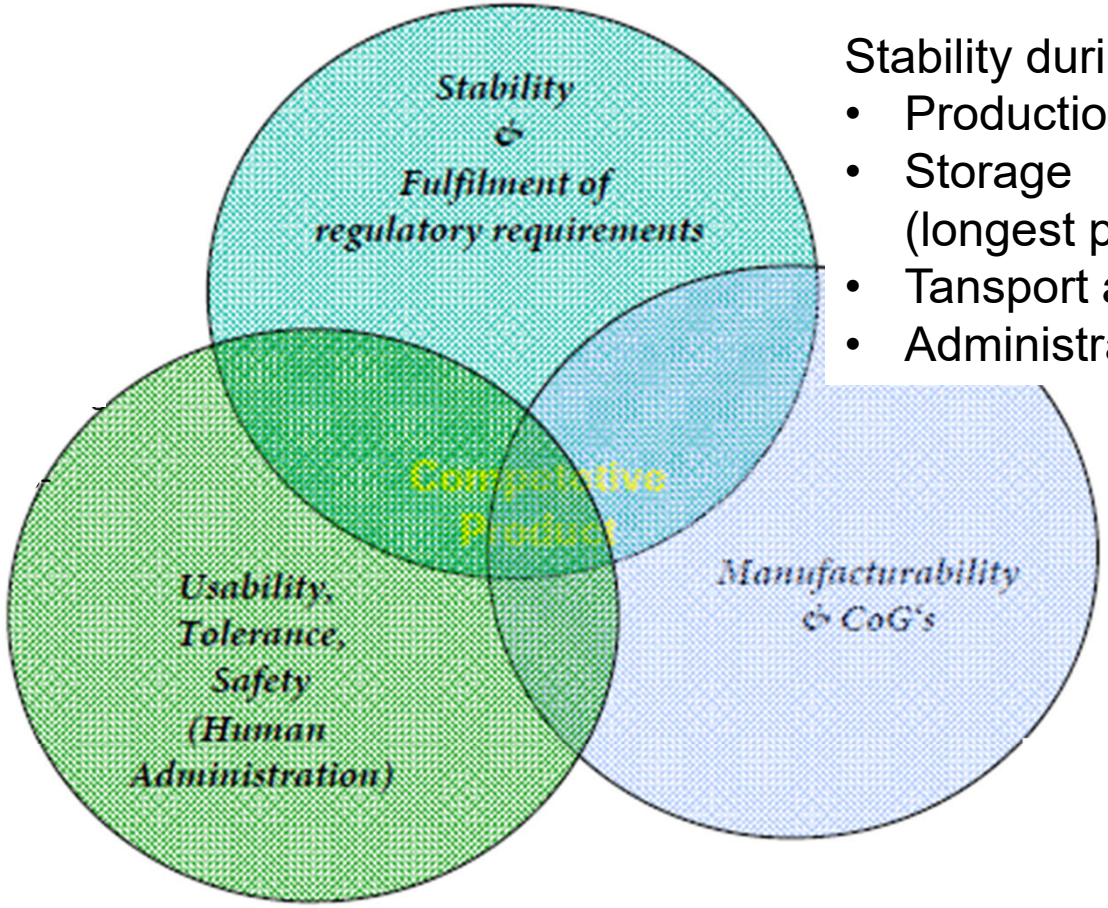
dents



splashing

fogging

Requirements of a formulation



Stability during:

- Production
- Storage (longest possible)
- Tansport and
- Administration

- Patient conveniene
- Patient adherence
- Dose delivery

Caveat for proteins: Influence on undesirable adverse events and clinical efficiency, immunogenicity and pharmacokinetic profile through product specific degradation products.

Design of a formulation

Buffer system

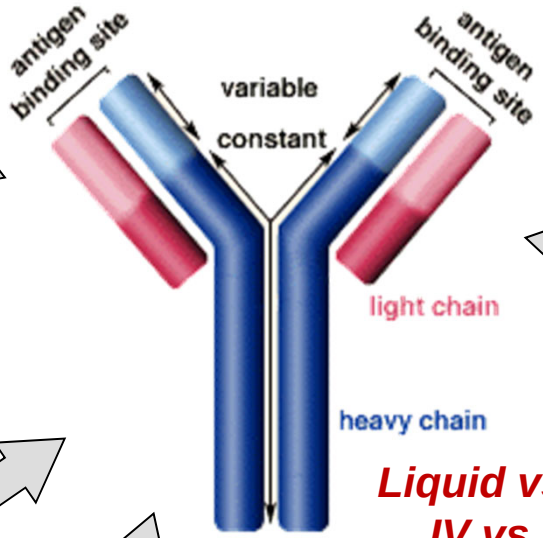
(His/HisHCl, Citrat, ~~Acetat~~)

~~Phosphat~~

Antioxidant (Methionine)

Preservatives (Multi-does-vials)

Benzylalcohol



Lyo/cryoprotectants and bulking agents (Sucrose, Mannitol, …)

Liquid vs. Lyo
IV vs. SC

Stabilizers during freezing/ thawing (Sucrose, Trehalose)

- tonicity adjusting agents at the same time

Surfactants (Polysorbate 20, 80, Poloxamer)

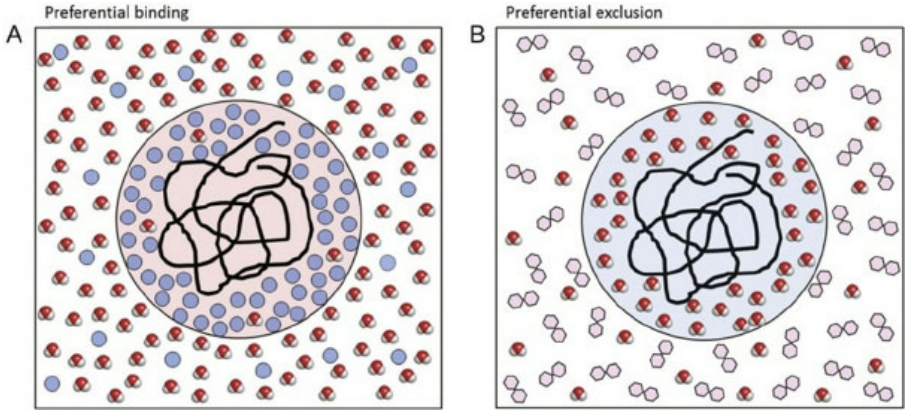
Viscosity reduction e.g. Arginine-HCl

Lyo/cryo-protective excipients

Cryoprotectant

Stabilizes during the freezing process

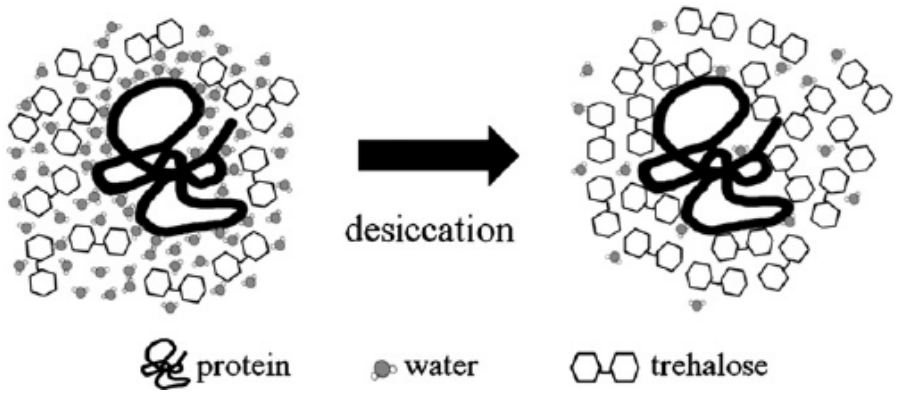
- Excipients are preferentially excluded from the surface of the protein. This is an thermo-dynamically unfavored state. As the unfolded state of the protein would enhance this state, the protein is stabilized.
- (Timasheff 1993).



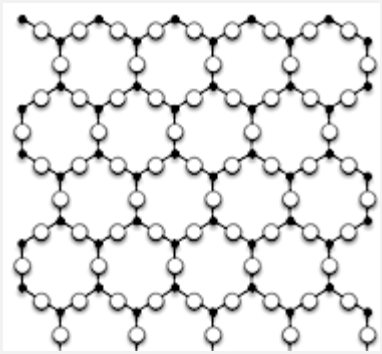
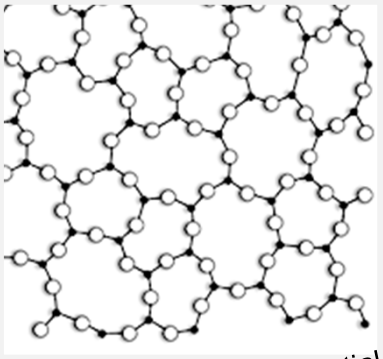
Lyoprotectant

Stabilizes during the drying process

- Water stablizes a protein in liquid solution by hydrogen bonding. The excipient replaces the hydrogen bonds of water during drying and thus stabilizes the protein.



Lyo/cryoprotective excipients

Crystalline excipients	Amorphous excipients
Ordered crystal structure 	Glassy state 
Eutectic temperature (defined melting point)	Glas transition temperature Characterization by differential scanning calorimetry

• Bulking agent
• High eutectic temperature :
  • Elegant cake appearance
  • Fast drying
	• Stabilzation of e.g. proteins
	• Acceptable bulking agent at the same time

• In many cases no stabilization (e.g. for most proteins) • Different morphologies dependent on excipient (Mannitol→ Annealing) • Glass breakage (Mannitol at high fill)	• Low glass transition temperatures → Cake structure?
Glycin, Mannitol, NaCl, …	Sucrose, Trehalose, PVP, Dextran, …

Examples

<u>Kadcyla 100 / 160mg</u>

20 mg/mL ado-trastuzumab emtansine
10 mM sodium succinate pH 5.0
60 mM D-Sucrose
0.02% Polysorbate

<u>Herceptin 150 / 400 mg</u>

25 mg/mL Trastuzumab
5 mM L-Histidine/-HCl, pH 6.0
60 mM D-Trehalose
0.01 % Polysorbat 20