



MedImmune

# **Dry Dosage Forms Produced by Vacuum Foam Drying**

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# Outline

- **Introduction**
- **Vacuum Foam Drying**
  - History
  - Process
  - Dosage form properties
- **Stability and Process Loss**

# Standard Dry Dosage Form for Vaccines Lyophilized / Reconstituted



BCG, measles, varicella, Hib, DTaP/Hib, meningococcal, MMR, MMRV, zoster, yellow fever, ...

# Novel Approaches to Vaccination

## Alternative Routes

- **Mucosal**
  - Ocular (drops)
  - Nasal (drops / spray / powder)
  - Pulmonary (liquid or dry aerosols)
  - Oral (liquid / pills / liposomes / microspheres)
  - Vaginal, rectal (creams)
- **Cutaneous**
  - Epidermal (powder, ballistic)
  - Liquid jet (liquid)
  - Topical (microneedles / patch / colloidal carriers)

## Alternative Processing / Stabilization

- **Spray Drying**
- **Vacuum (Freeze) Foam Drying**

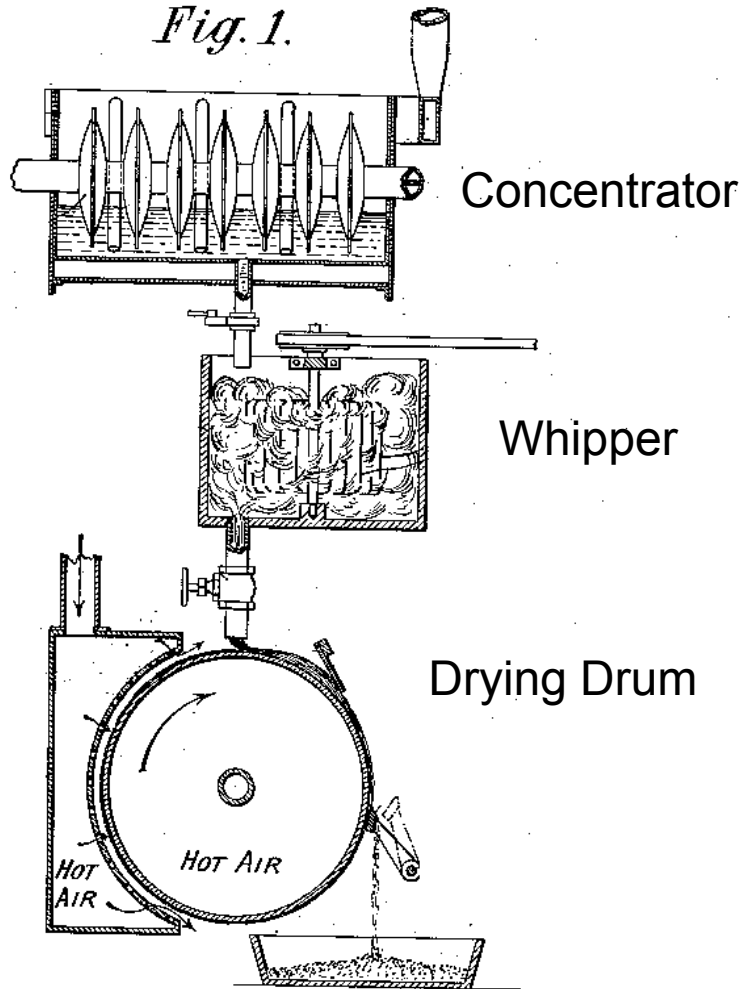
# History of Foam Drying: Drying of Milk in 1917

G. H. CAMPBELL.  
DRYING MILK.  
APPLICATION FILED DEC. 29, 1913.

1,250,427.

Patented Dec. 18, 1917.

*Fig. 1.*



- Foam drying is an established technique in the food industry
- Key features were recognized early
  - Concentration step
  - Foaming
  - Drying on drum or belt
  - Fast reconstitution



# Vacuum Foam Drying in the Food Industry

2,328,554

## **POROUS EXPANDED CITRUS FRUIT PRODUCTS**

**Wilbert A. Heyman, New York, N. Y., assignor to Granular Foods, Inc., New York, N. Y., a corporation of Indiana**

**No Drawing. Application March 25, 1941, Serial No. 385,077**

As will be more specifically described hereinafter I form the product of my invention by grinding the complete lemon, extracting only the deleterious seeds and stems. The ground lemon including the skin, is then mixed with corn syrup and formed into a powder by boiling the corn syrup under high vacuum until the water vapor bubbles forming in the gradually solidifying mixture expand the mass and finally burst into one another to form an expanded intercommunicating cell structure which is thoroughly dehydrated by continued heat and vacuum. The dehydrated and expanded mass is then broken down and ground to particle or powder size as desired.

- “Puff-drying” was established for food products in the 40’s
- Department of Agriculture (Eastern Utilization Research and Development Division) developed vacuum foam drying of whole milk in the 50’s and 60’s



# Preserving Biologicals by Vacuum Foam Drying



- Douglas I. Annear stabilized various bacteria by vacuum foam drying on peptone plugs in the 50's.
- Commercialized in the 90's (Universal Drying Technology, Victor Bronshtein; Quadrant Healthcare, Bruce Roser) Now VitriLife®; Avant Immunotherapeutics

Annear, D. I.: (1954) *Nature* **174**, 359; (1956) *Journal of Hygiene* **54**, 487; (1966) *Nature* **211**, 761; (1970) *Journal of Hygiene* **68**, 457.

# Vacuum Foam Drying Steps

- Preconditioning
- Bubble formation (boiling)
- Foam formation
- Foam desiccation / foam aging



# Bubble Formation



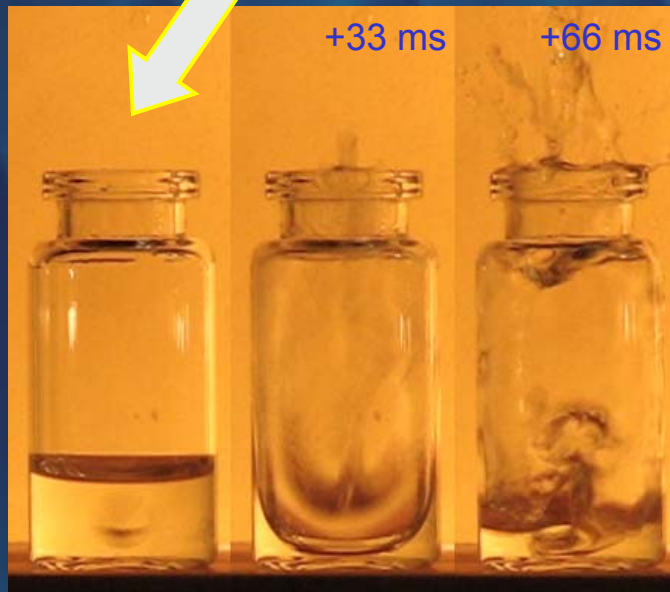
- Precondition to set viscosity and surface tension of solution
- Drop pressure below saturation pressure of the solution
- Heterogeneous bubble nucleation
- Bubble rising and inflation

- **Common problems**

- Violent boiling / splattering
- Inconsistent onset of bubble nucleation

- **Suggested solutions**

- Mixing
- Chamber rotation
- Seed crystals
- Ultrasound
- Entrained gases



# Foam Formation



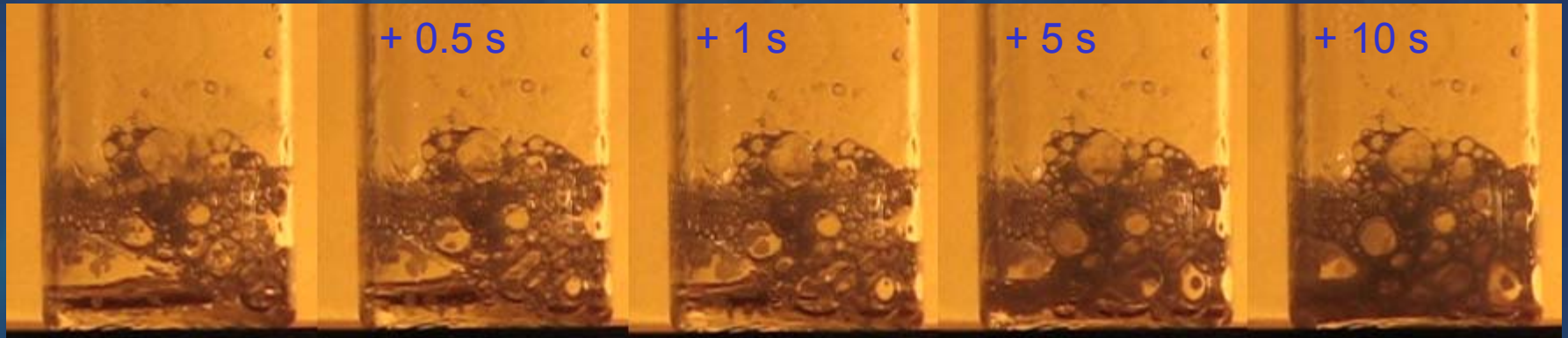
viscosity



- Bubble inflation is arrested by increasing membrane viscosity
- Membranes and foam cells rupture and collapse repeatedly until foam is stabilized.
- Process depends on
  - P, T
  - Container geometry
  - Surface tension
  - Viscosity
  - Bubble nucleation and growth rate



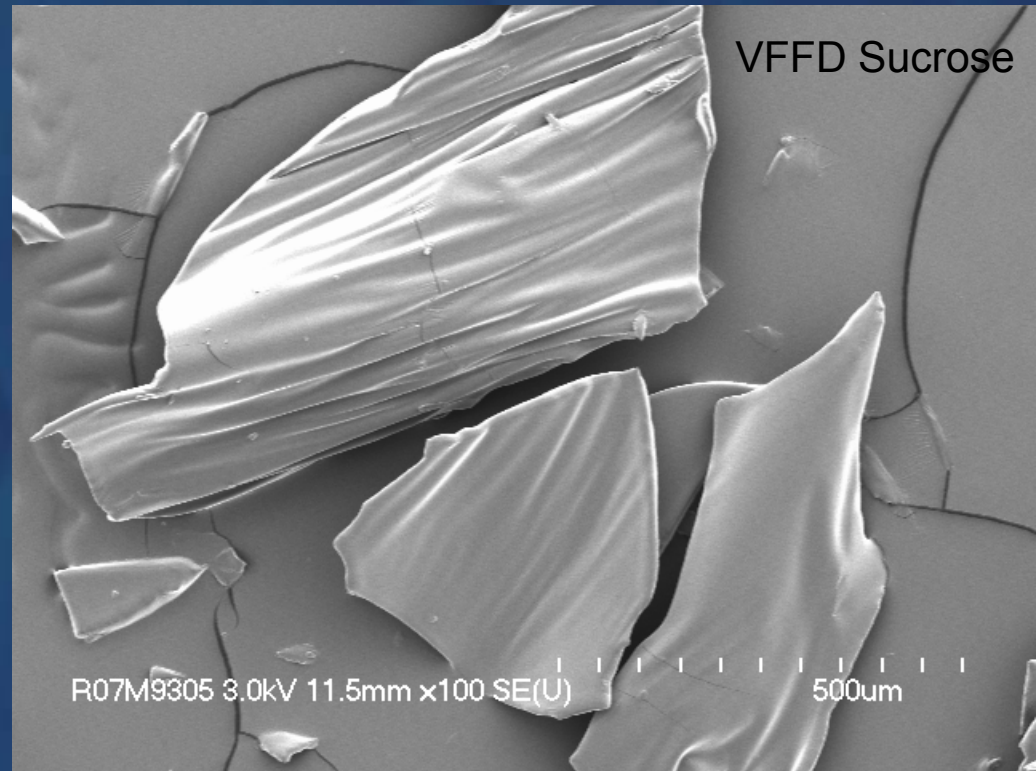
# Foam Aging



- **Foam ages by draining and coarsening**
- **Foam aging slows down because of**
  - Desiccation → increase in  $T_g$  (Vacuum Foam Drying)
  - Evaporative cooling → freezing (Vacuum Freeze Foam Drying (VFFD))



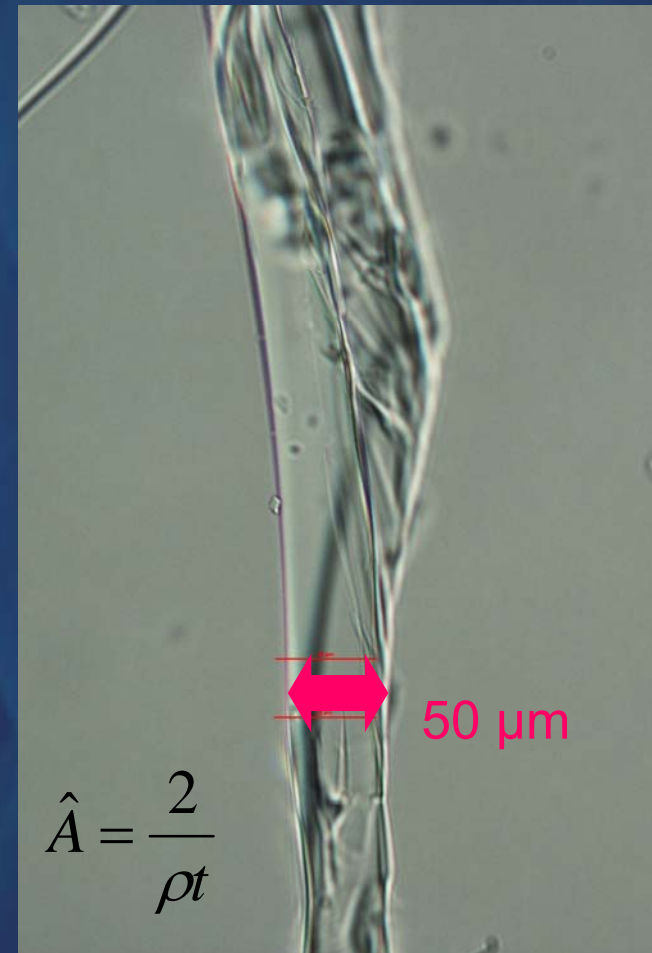
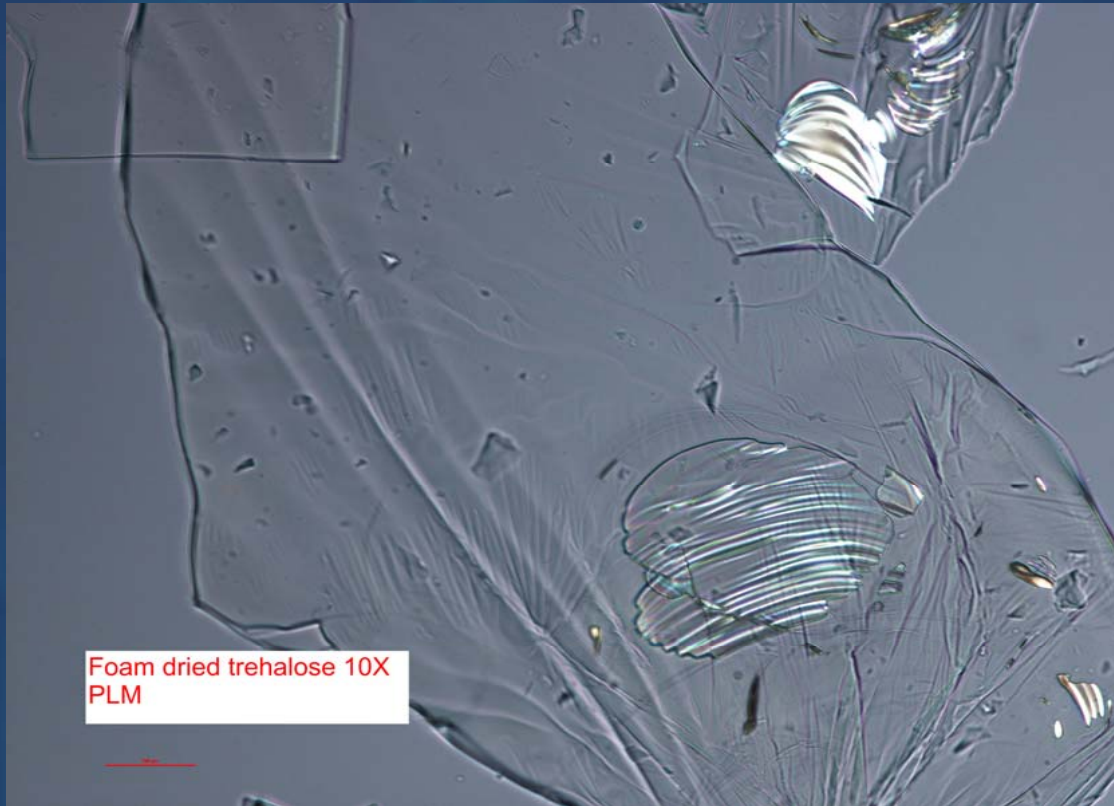
# Foam Desiccation



Specific Surface Area: 0.06 m<sup>2</sup>/g

- Foam desiccated under collapse conditions (Drying temperature above glass transition temperature)
- Results in low specific surface area

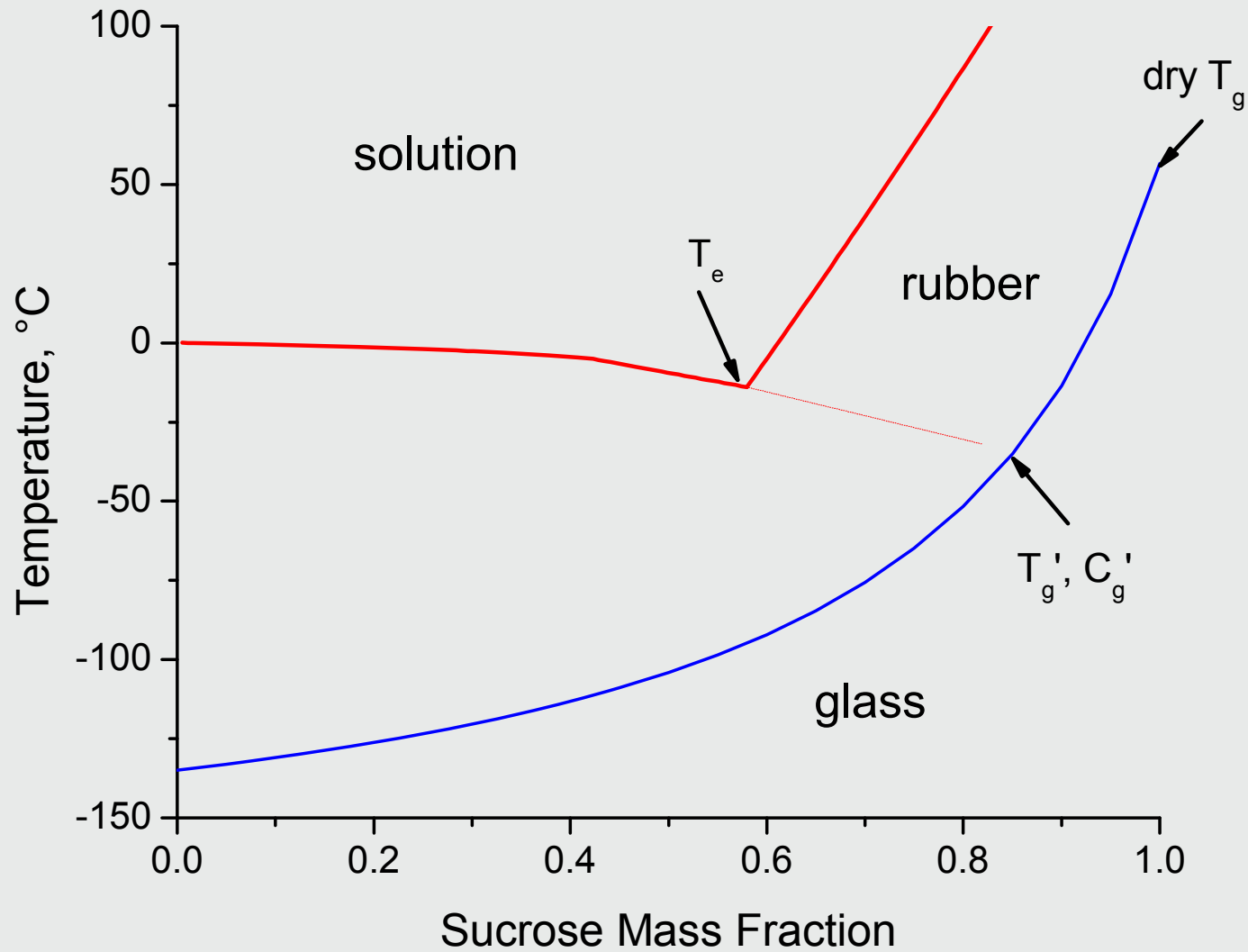
# Foam Structure



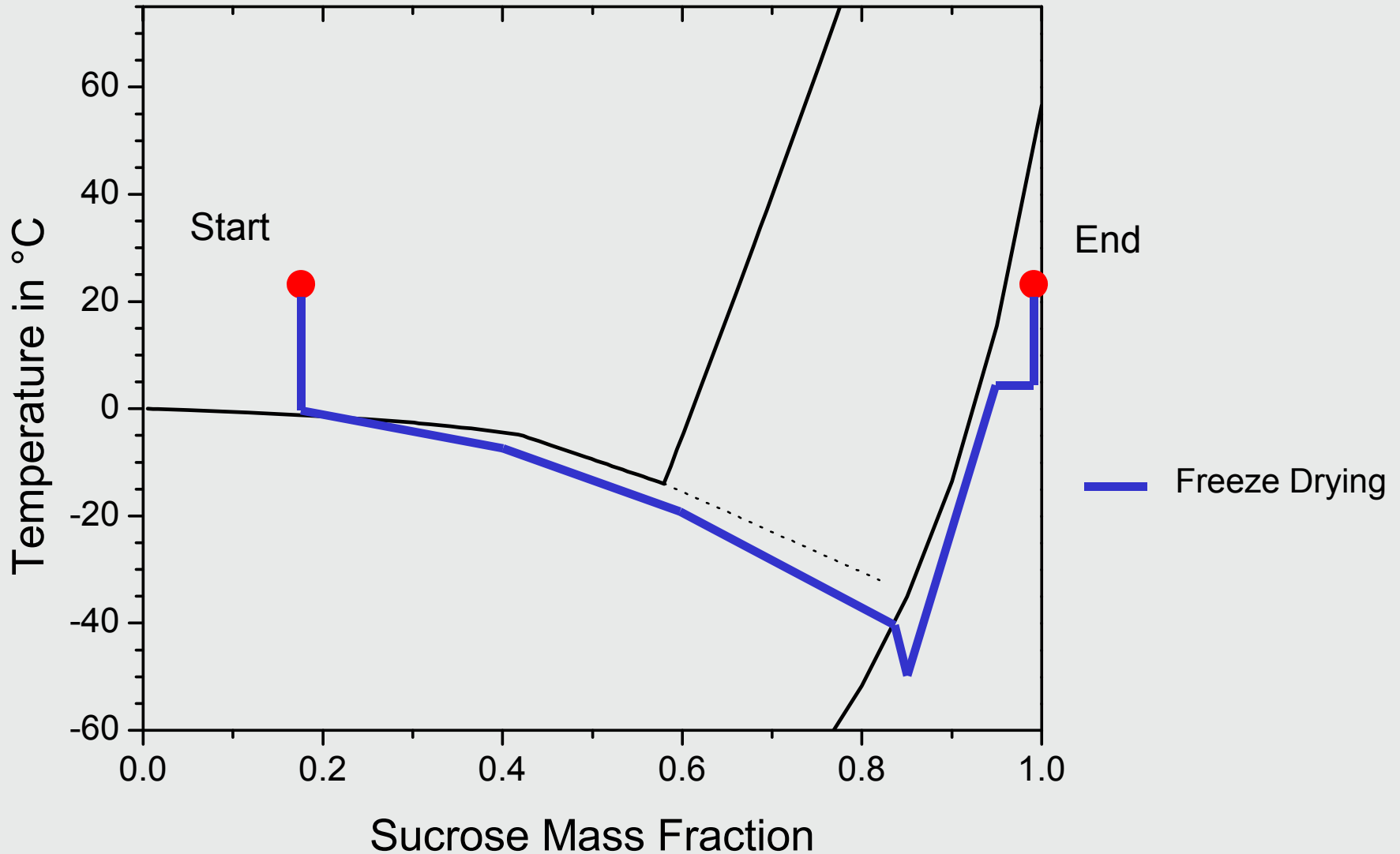
- Foam can be modeled as non-porous, thin membranes
- Specific surface area lower than lyo-cake
- Inhomogeneous structure
- Control of membrane thickness is important



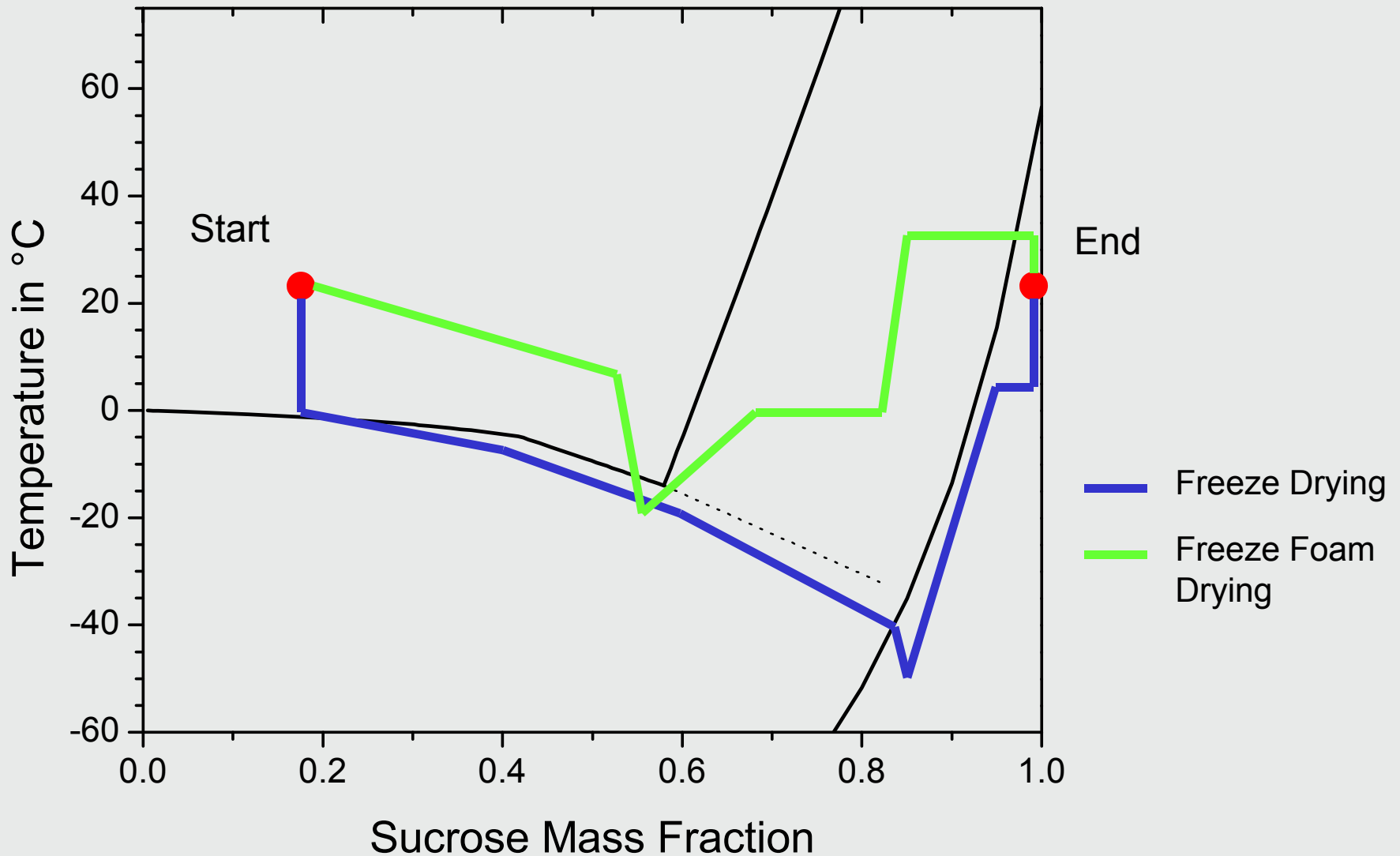
# Sucrose Water State Diagram



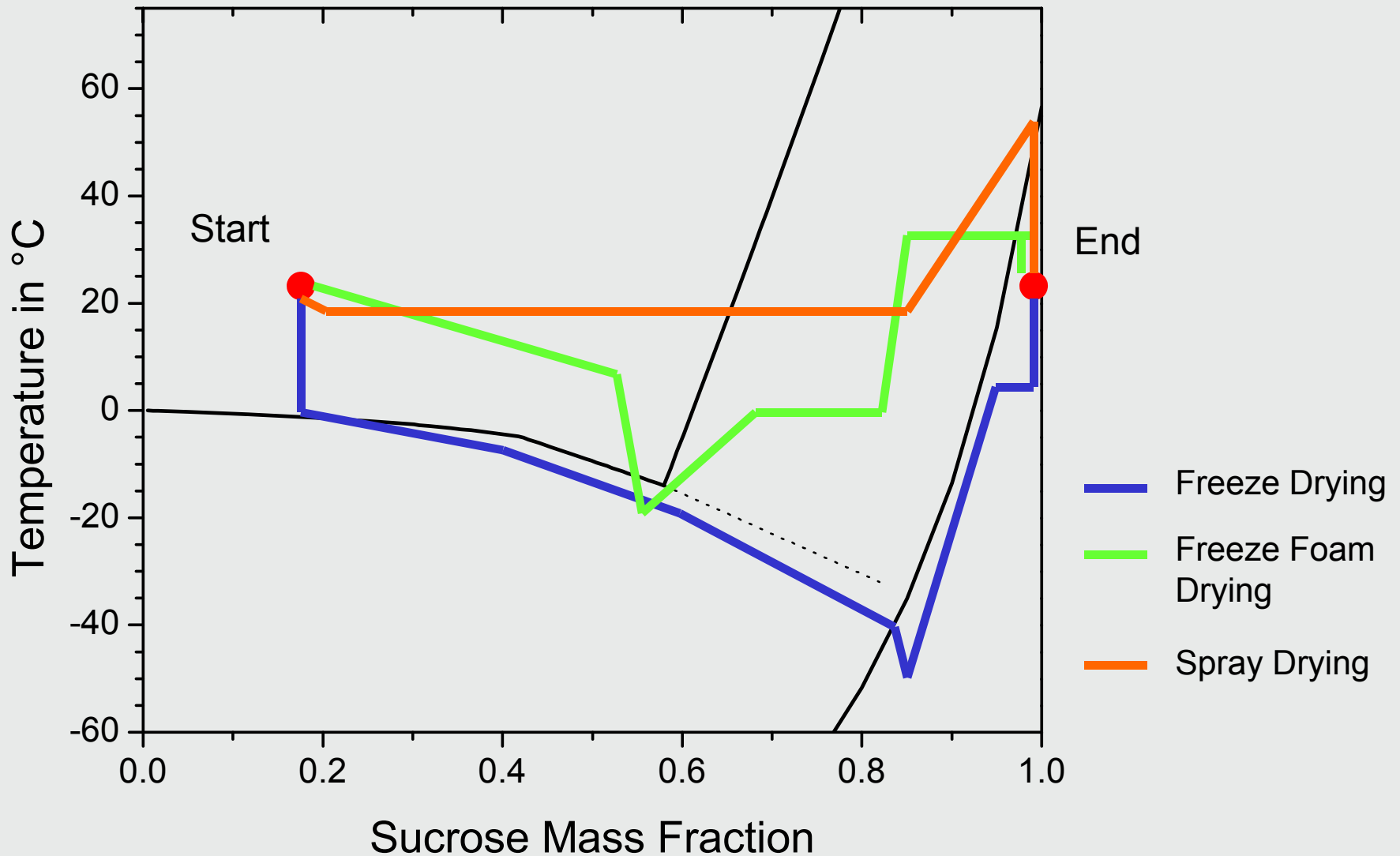
# Drying Process Comparison



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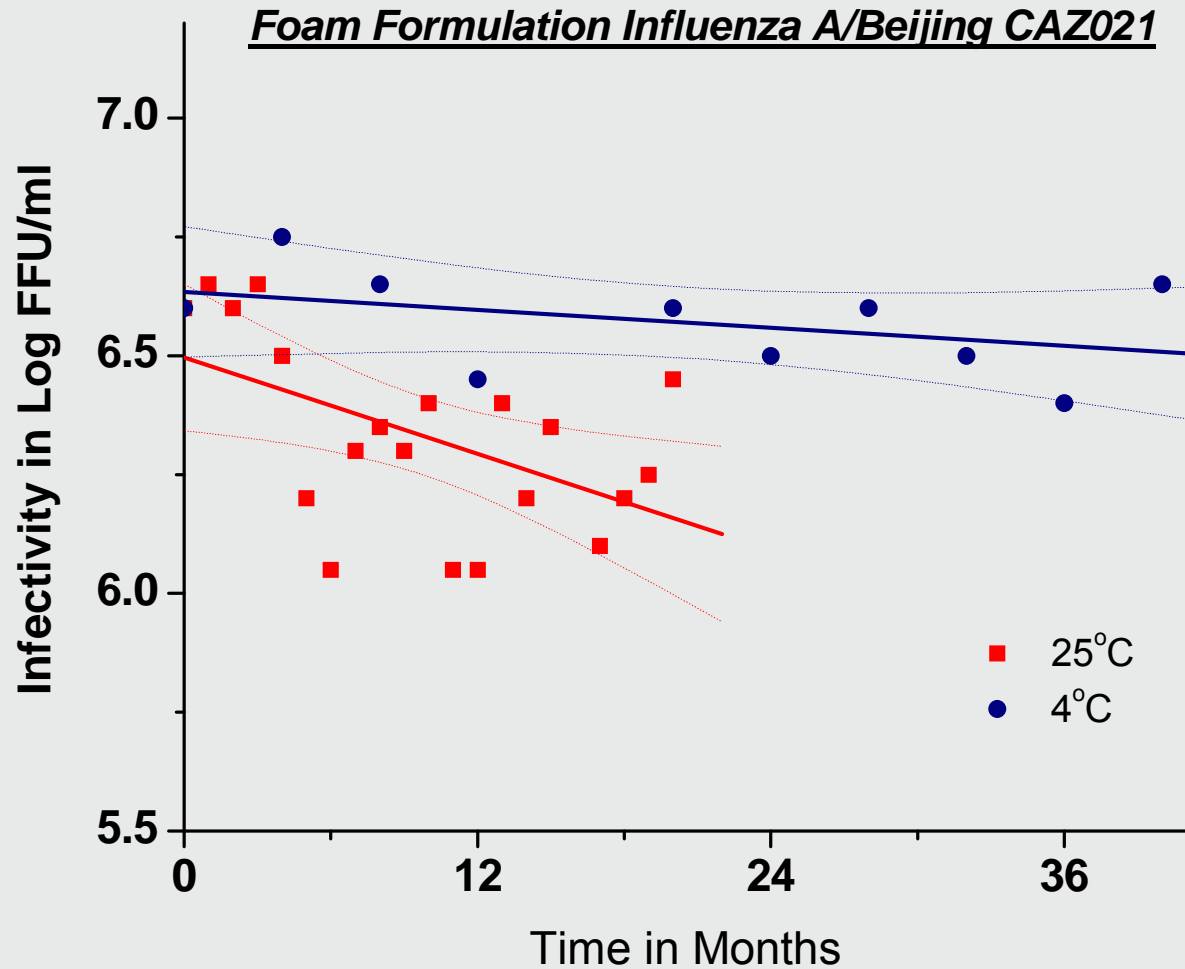
# Dried Foam Characteristics

- **Low specific surface area**
  - Much lower than lyo-cake
  - Much lower than typical spray dried powder
  - Slow water release and uptake
- **Relaxed glass**
  - Different glass properties and crystallization propensity compared to spray dried or freeze dried glasses

Connection to stability still unclear



# Stabilization of Live Attenuated Influenza Vaccine



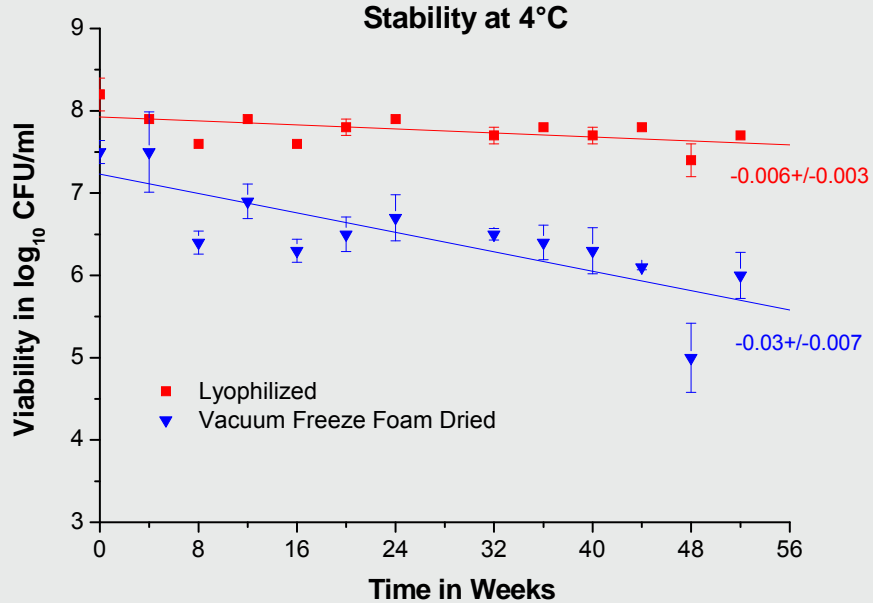
Long-term stability during refrigerated and room temperature storage.

# Stabilization of Live Attenuated Influenza Vaccine

	4°C		25°C	
	Slope	Time to 1 Log loss	Slope	Time to 1 Log loss
Formulation A/Beijing	-0.003+/-0.002	> 20 y	-0.017+/- 0.006	> 4 y
Formulation A/Sydney	-0.005+/-0.002	> 15 y	-0.020+/-0.006	> 4 y
Formulation B/Harbin	-0.009+/-0.002	> 9 y	-0.023+/-0.005	> 3 y

Excellent long term stability for different influenza vaccines

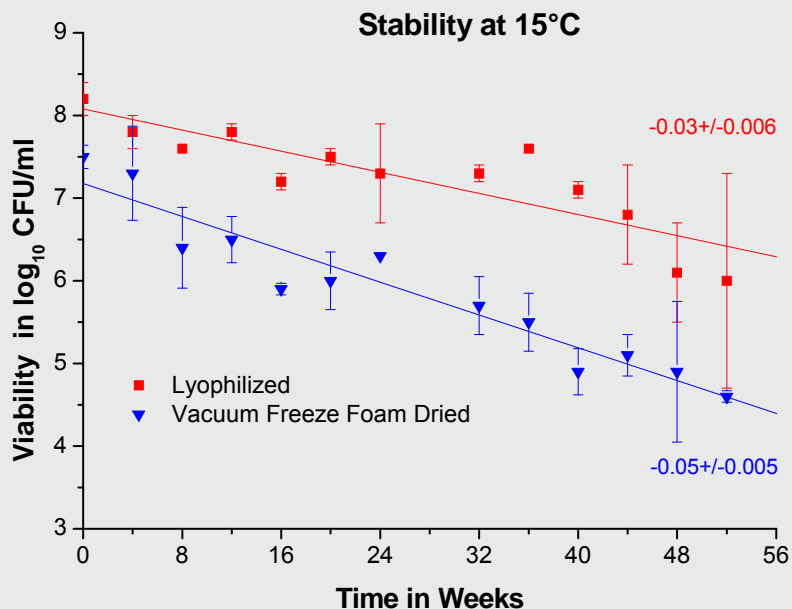
# Stabilization of a Bacterium



- Identical formulations of *listeria monocytogenes* processed by lyophilization and vacuum freeze foam drying

- Lyophilized dosage form has better stability and lower process loss

- Stability advantage of foam drying is not universal



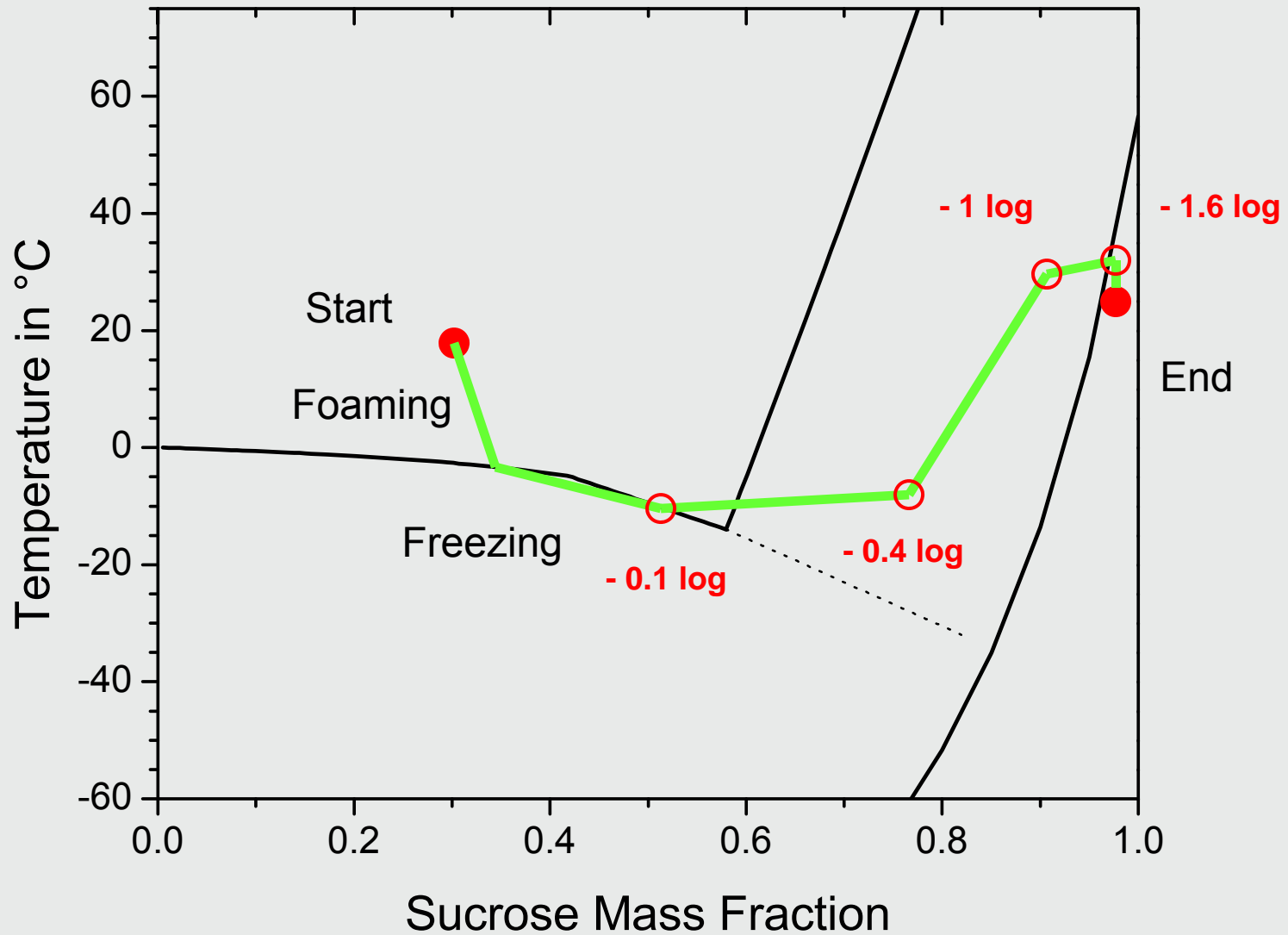
# Process Loss during Foam Drying

Comparatively large process loss is often observed in foam drying.

Potential loss mechanisms:

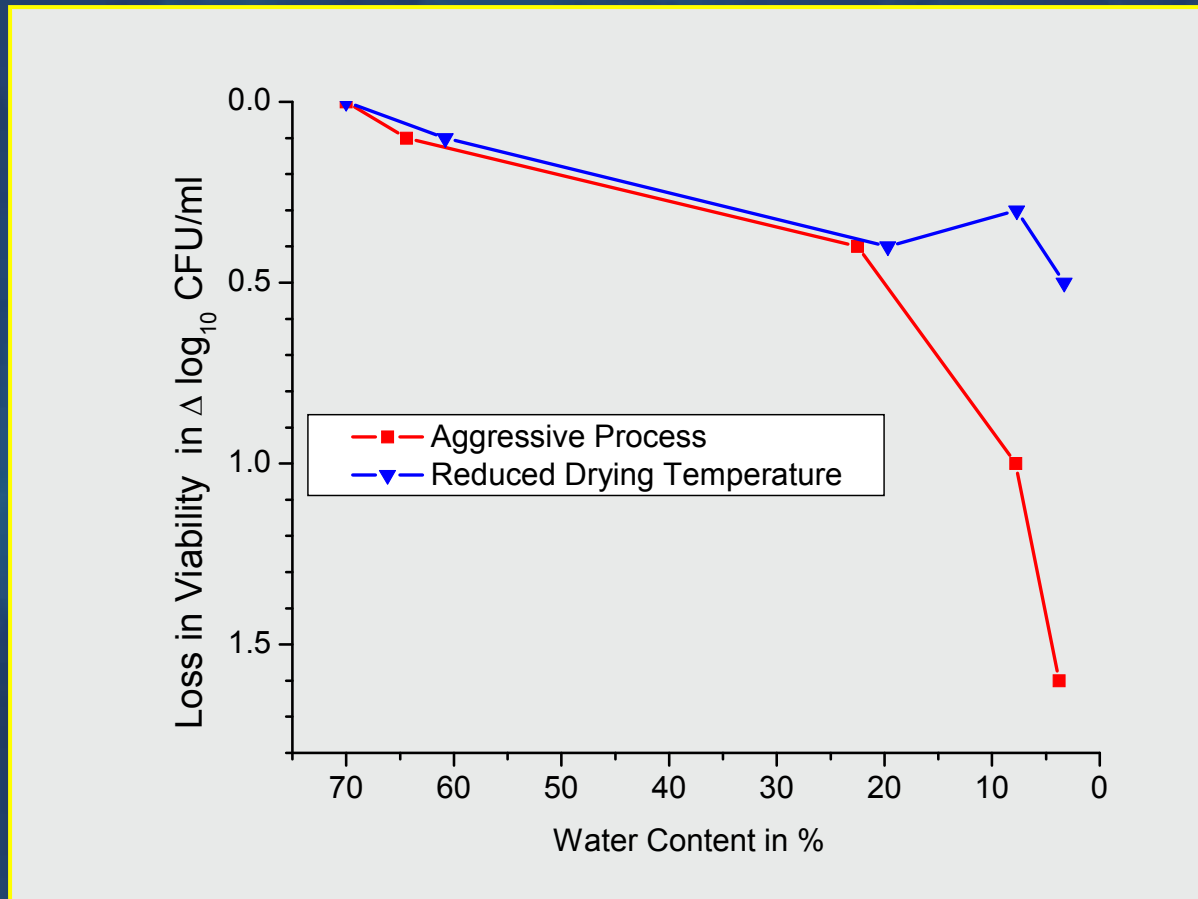
- Boiling – high shear forces, cavitation.
- Foaming – rapid and repeated change of local environment.
- Freezing – repeated freeze thaw with varying freezing rates.
- Drying under collapse conditions– desiccation and temperature stress.

# Process Loss Tracking





# Process Modification Reduces Loss



- Identical formulations of *listeria monocytogenes* processed using two different vacuum freeze foam drying cycles
- Significant improvements can be achieved by modifying drying temperatures for partially desiccated foam

# Summary

- Vacuum foam drying provides superior stability for some biologics such as live attenuated virus vaccines.
- The stability advantage is not universal and not well understood.
- Process loss can be significant and was attributed to a combination of desiccation and temperature stress for a bacterium.
- Process loss during foam drying can be reduced by cycle optimization.
- Controlling foam structure is key to process control.