Advances in Spray Freeze-Drying for Uniform Bulk Intermediates and Lyo Products

Prof. em. Dr. Hans Leuenberger U of Florida
(hans.leuenberger@ufl.edu)
Howard Stamato (howard.stamato@gmail.com)
Bernhard Luy (bernhard.luy@meridion-technologies.de)

Nov 12th 2019

Outline

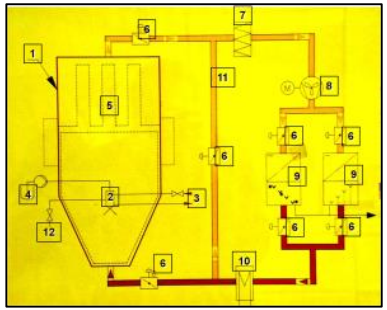
- **Background** (Concept & Technology)
- **Process Principles ,Technologies & Modeling**
- **Industrial Case Study**
- **Impact of Technology on**
  - **Process**
  - **Product Innovation**
  - **Manufacturing Logistics**

Need for new Processing Techniques ?

→ Based on need for new product presentation
as compared to conventional Lyo-Cakes

- increasing demand for protein-based products such as MAB's, Vaccines, Gene Therapy
- protein solutions: stability challenges → lyophilization is a common process
- cold chain handling has risks (e.g. auto-injections require cold-chain compliance at patients → proven deficits are identified)
- conventional lyo: long and rigid supply chain (liquid filling followed by lyo) vs
- homogeneous bulk availability: filling follows lyo, i.e. after stabilization → filling from bulk as per requirement → huge gain in flexibility
- flexibility in supply chain assures availability to patients

Technology Development Background



Research Project at the University of Basel (1980‘s)

Atmospheric Spray Freeze Drying in Fluidized Bed Operations

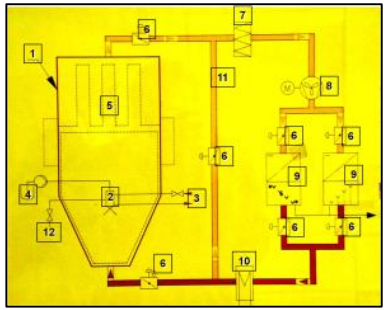
- Started in 1980s (in cooperation with Glatt AG, Switzerland); 4 PhD thesises (A. Kahn, M. Mumenthaler, H.P. Mennet and Mathias Plitzko) until mid 90‘s leading to patents as part of the 12 patent families of the Glatt Group with the name Hans Leuenberger as inventor.

- **Result: a 3 step process required**

- spray freezing phase at T_{AIR} < -60°C in the fluidized bed (FB) tower Nr. 1
- primary drying phase at T_p <-10° C in the subsequent FB tower Nr.2.
- secondary drying phase at T_s = ambient temp. in the FB tower Nr.3

However, the patent based on a quasi-continous process separating the spray-freezing step from the subsequent drying processes was not implemented by the Glatt group.

Technology Development Background



The quasi-continuous patent (US 6,584,782 B2, July 1, 2003) of the Glatt group was not commercialized for the following reasons:

- ***very low water uptake of cold air***
- → very long drying times, excessive air flow; „filter drying“ required due to freezing requirements (high air velocity)
- product movement by air fluidization possible, but **less efficient in large scale** (design constraints)

Conclusion: ‚Single pot processing‘ not feasible,
but need to separate the spray-freeze drying process into **two process steps** , i.e.

1. **particle formation** and
2. **dynamic bulk freeze drying**

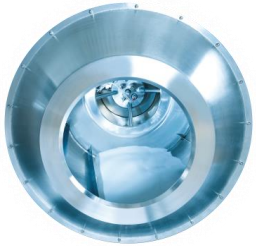
which was successfully realized by MERIDION

Spray Freezing & Dynamic Bulk FD

Two new process steps:

Spray Freezing: *Generation of homogeneous frozen bulk*

Frozen microspheres are generated as bulk by dispersing the substrate liquid using frequency nozzles into single droplets, which by gravity pass through a cooling zone, congealing to frozen spheres (ambient pressure).



Dynamic Bulk Freeze Drying: *Lyophilization of frozen bulk*

frozen bulkware is lyophilized in a rotational vacuum freeze dryer under constant gentle mixing. Sublimation energy is transferred by radiation and temperature controlled surfaces.

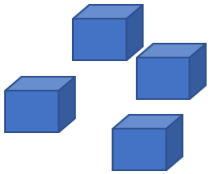
Comparision of Concepts

Conventional Lyophilization

Protein Expression tank

Bulk Solution

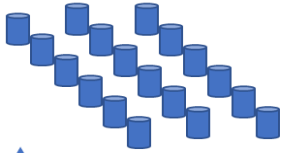
Fill /Freeze intermediate containers



Thaw/Mix/ Adjust tank

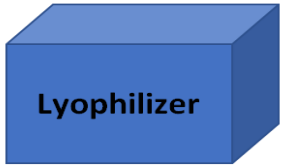
Bulk Solution

Fill vials, unit dose



Unit Dose Determined

Freeze/Dry/Seal vials in chamber



More stable dry product

Final Product

Final Packaging

SPRAY FREEZE DRYING

More stable dry product

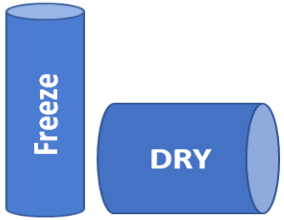
Unit Dose Determined

by bulk SFD, the two steps get reversed

Protein Expression tank

Bulk Solution

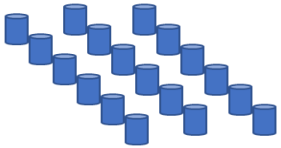
Freeze/Dry pellets in chamber



Bulk Product intermediate container

Dry Pellets

Fill vials, unit dose



Final Product

Final Packaging

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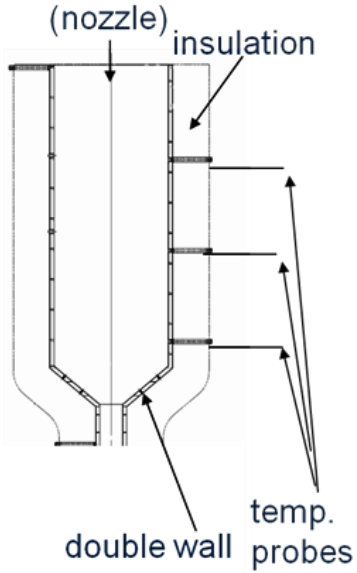
Spray Freezing Process for the Generation of Frozen Bulk

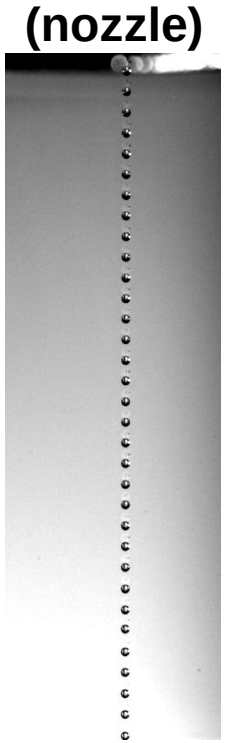
- **cooling of process gas (-80 … 140 °C) via double wall by LN_2 / GN_2→ aseptic processing suitability w/o need for sterile LN_2**



Spray Freezing Chamber
(Lab size, stand alone)

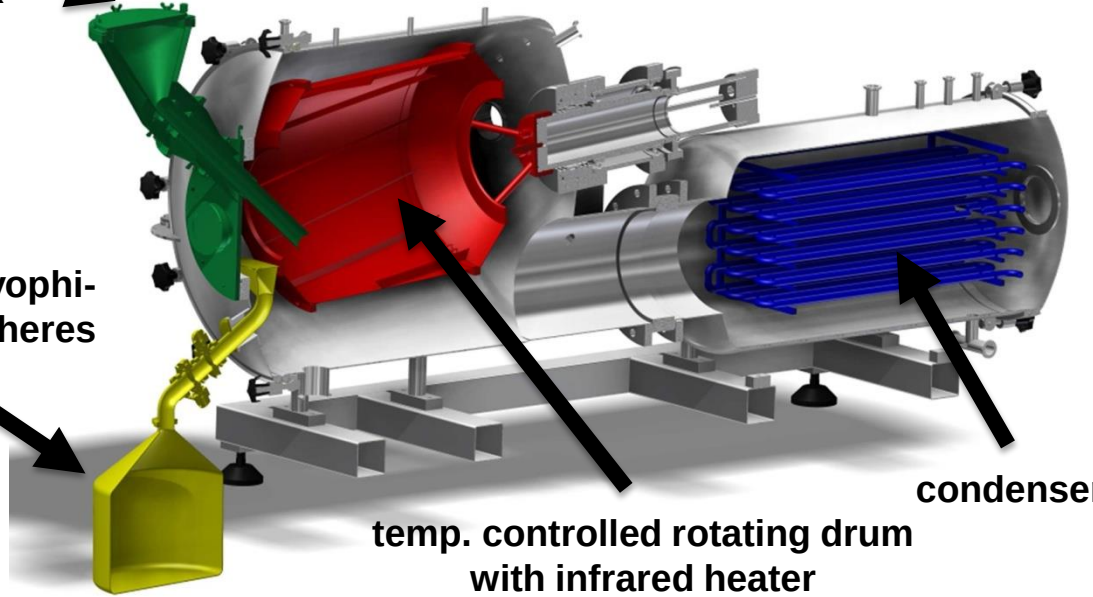
Top View
w. lid & nozzle

Droplet Generation by Controlled Laminar Jet Break up



- droplet generation by (resonance) frequency (low shear/low pressure to avoid mech. stress)
- droplet size selectable: from ca. 300 µm ….. 1000 µm
- throughput depends also on droplet size
- need for deflection of droplet pattern
  - to avoid coalescence
  - to increase spray rate / nozzle
- formulation requirements: solid content for mechanical stability in dynamic SFD: > 5 …10% (up to 40%)

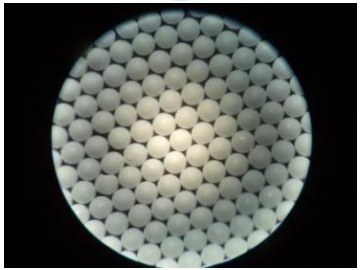
Dynamic Bulk Freeze Drying in a Rotating Drum



LabScale dryer
as stand-alone unit

Dynamic Bulk Freeze Drying in a Rotating Drum

Design & Process characteristics:

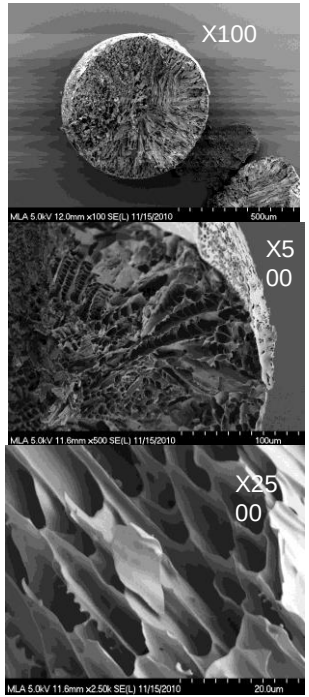


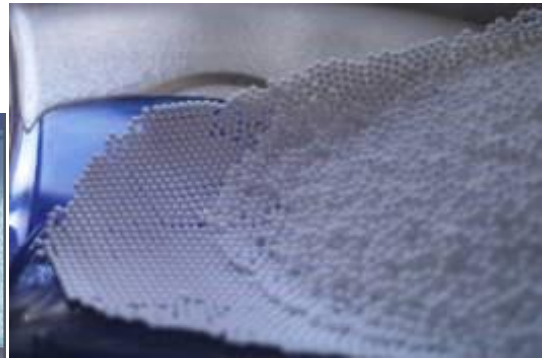
- **rotating drum is operated under FD conditions**
  (e.g. down to 20 µbar)
- **drum w. IR radiator and double wall to control surface temp.** (sil. oil, e.g. -55 …. +55°C)
- **direct measurement of bulk temperature**
  with constant gentle mixing (no milling or sieving)
- **homogeneous conditions**
  → the process provides for product homogenity due to homogeneous process conditions for the entire batch
- **formulation requirements** to provide for mechanical stability

Dynamic Bulk Freeze Drying in a Rotating Drum

typical product & process properties:

- **good flowability**
  electrostatics may occur but can be controlled by process conditions
- **residual moistures < 1%**
- **typical bulk densities ca. 0,2 – 0,4 g/cm³**
- **drying times load dependent 5 hr …. 25 hr**
- **particle size vs vapour flow**
- **final bulk product consists of lyophilized spheres**

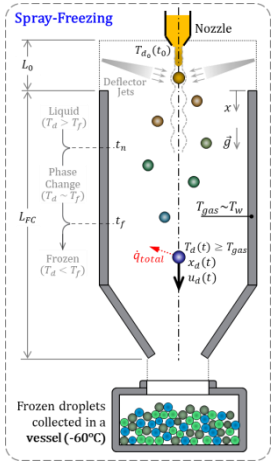


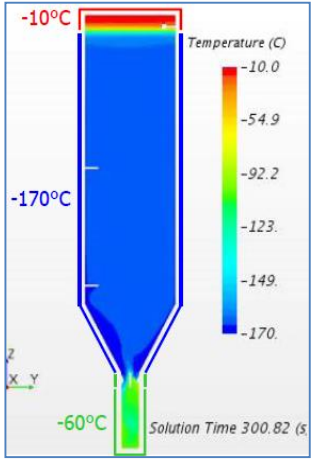


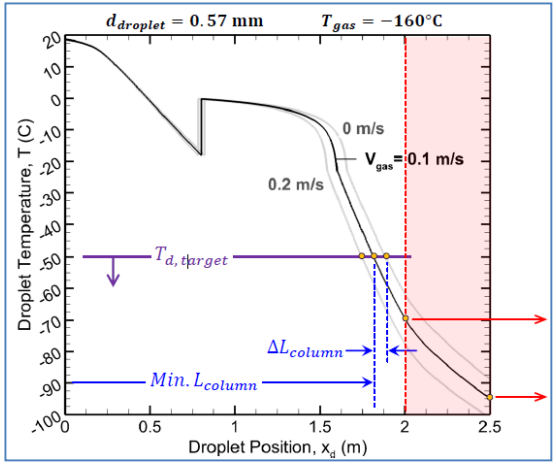
Modeling of SFD Processing

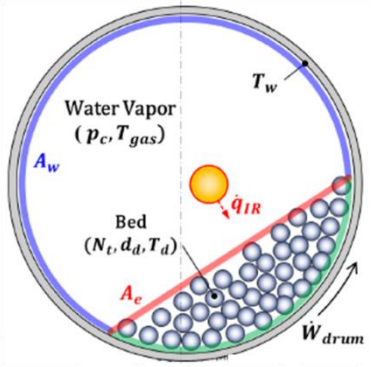
- Modeling of both
  Spray Freezing (completed)
  and
  Rotary Freeze Drying (ongoing)
- in freezing, the avg. product temp. can vary ± 8K due to oscillation of V_{gas}
- the model can predict the column length required to freeze droplets below a target temperature

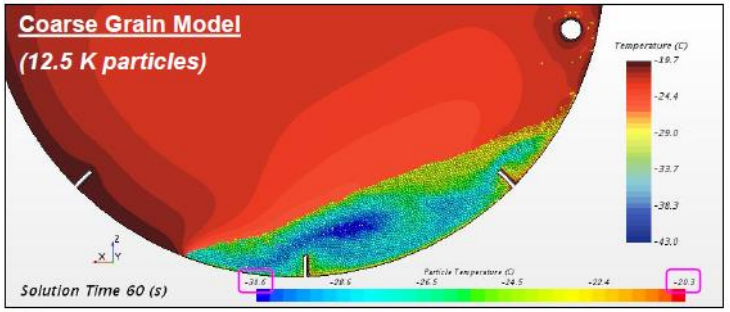
More details:
Sebastiao, Bhatnagar, Tchessalov, Ohtake, Plitzko, Luy and Alexeenko:
JPharmSci 108(6), 2063-2085, 2019







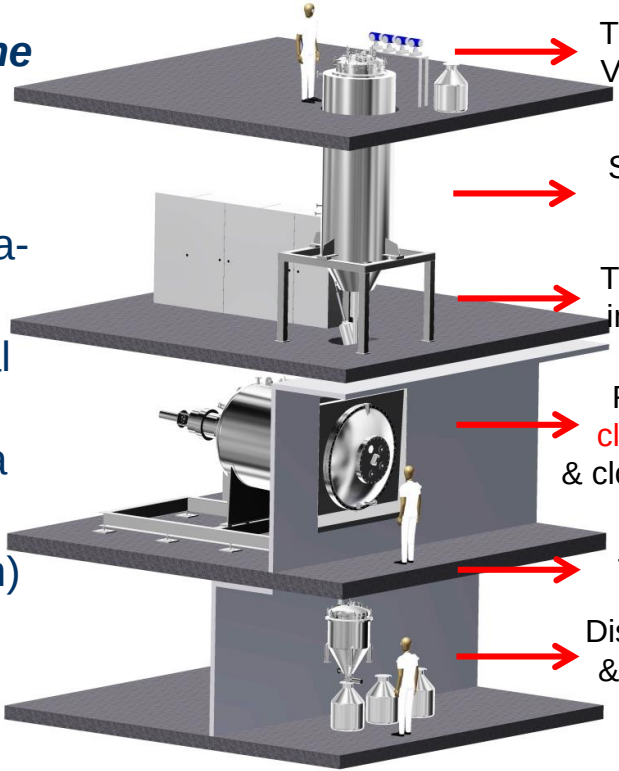




SFD Process Line, Industrial Scale (aseptic processing)

Integrated 100L Manufacturing Line for Aseptic SFD of Microspheres

- integration of two main process steps: particle generation & dynamic freeze drying incl. transfer
- product flow by gravity & internal drum discharging; no need for loading/ unloading in sterile area
- process line with total containment incl. WiP/CiP & SiP (steam)
- no open handling of product: room classification (cost impact, e.g. on analytics)



Transfer Liquid Vessel : Nozzle

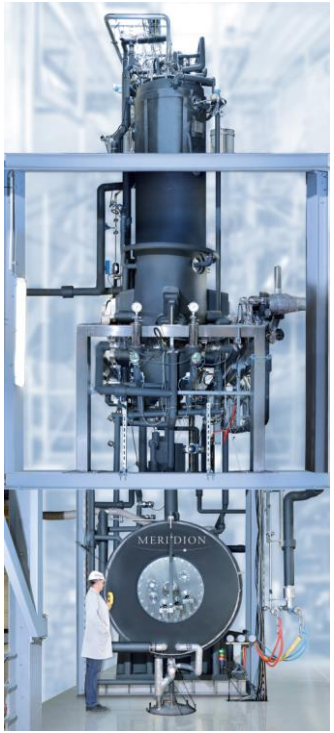
Spray freezing chamber

Transfer to dryer, incl. vacuum flap

Rotary FD w. closed charging & closed discharging

Transfer tube

Discharge vessel & filling of IBCs



Industrial Applications for Specialty Chemicals

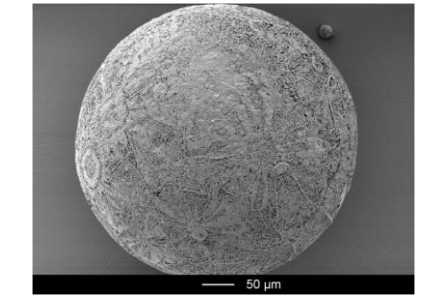
Rotary Freeze Dryers in 24/7 operation, for a nanoparticle based consumer electronics product

Multiple drying units suggest a method for continuous manufacture

Lyophilized Bulk: Product Innovation Potential

Summary (I)

SFD products allow for :

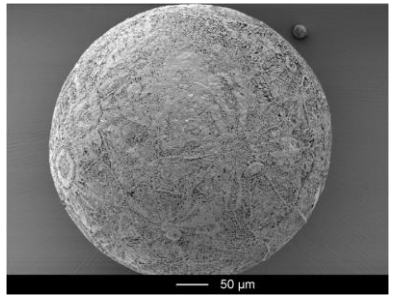


- high homogeneity (e.g. nucleation uniformity) & physical properties allow for filling accuracy
- high protein concentrations (tested up to 200 mg/ml)
- reduction of reconstitution time due to large surface
- cake appearance / inspection
  „multiparticulate dosage form“ vs. one lyo-cake
- filling of different products (‚compounding on filling line‘)
- Solid Dos. Form technologies applicable (e.g. coating, ODT formulations)

Lyophilized Bulk: Innovation Potential in Logistics

Summary (II)

Free flowing, homogeneous lyophilized bulkware allows for :



- filling on demand (independent of liquid prep. process)
- dosing flexibility
- primary packaging flexibility
- time to market / patient reduction
- avoidance of cold chain requirement
- → physical properties are prerequisite for subsequent filling; technologies tested & available

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Acknowledgements

Séb. Trichot / Fréd. Georges
Sanofi Pasteur France

I. Borges Sebastiao / S. Tchessalov / B. Bhatnagar
Pfizer Inc BioTher. PhRD

Alina Alexeenko
Purdue University

Matth. Plitzko, Th. Gebhard
Meridion Technologies Germany

Thank you! & What do you prefer?

Patel SM et al. Lyophilized Drug Product Cake Appearance: What Is Acceptable?
Journal of Pharmaceutical Sciences Volume 106, Issue 7, July 2017, Pages 1706-1721
Do you need a 100% inspection of the cake in your vials?

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