Continuous freeze-drying and its relevance to the pharma/biotech industry

Original
Continuous freeze-drying and its relevance to the pharma/biotech industry / Pisano, Roberto; Capozzi, Luigi C.; Trout, Bernhardt. - ELETTRONICO. - (2017), pp. 1-26. ((Intervento presentato al convegno Integrated Continuous Biomanufacturing III tenutosi a Cascais (Portugal) nel September 17-21.

Availability:
This version is available at: 11583/2701006 since: 2018-02-22T09:51:17Z

Publisher:
ECI Symposium Series

Published
DOI:

9-19-2017

Continuous freeze-drying and its relevance to the pharma/biotech industry

Roberto Pisano
Politecnico di Torino, roberto.pisano@polito.it

Luigi C. Capozzi
Politecnico di Torino

Bernhardt Trout
Massachusetts Institute of Technology

ICB III 2017 – Integrated Continuous Manufacturing III
September 17-21, 2017, Cascais, Portugal

Continuous freeze-drying and its relevance to the pharma/biotech industry

Roberto Pisano
Department of Applied Science and Technology
Politecnico di Torino

Introduction

Freeze-drying /Lyophilization is

a process where water, or another solvent, is removed from a frozen solution at low temperature and pressure via sublimation

A freeze-drying cycle encompasses three steps

- Freezing
- Primary drying
- Secondary drying

Almost 50% of biopharmaceuticals listed by FDA and EMA is lyophilized, proving that freeze-drying is the preferred way to stabilize large molecules that are not stable in liquid, despite its high energy consumptions and long processing time.

Introduction

Freeze-drying of pharmaceuticals is performed batch-wise

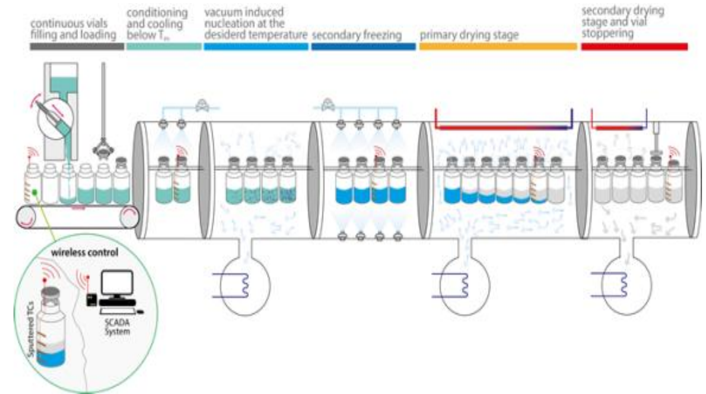
- Long and expensive process
- Heat and mass transfer is not uniform within the batch of vials
- Heterogeneity in freezing behavior
- Heterogeneity in drying behavior
- Poor control of product quality

vial-to-vial heterogeneity

Examples of lyophilized samples belonging to the same lot of production

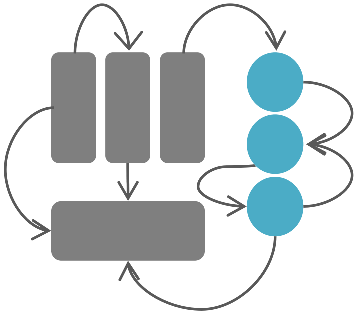
Background & Problem statement

Blue-sky thinking
Continuous Manufacturing



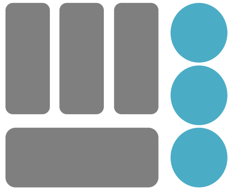
Seamlessly integrated & full characterized process

QbD & PAT



Understanding role and impact of individual steps

Traditional
Batch
Manufacturing



Disconnected process steps

Past

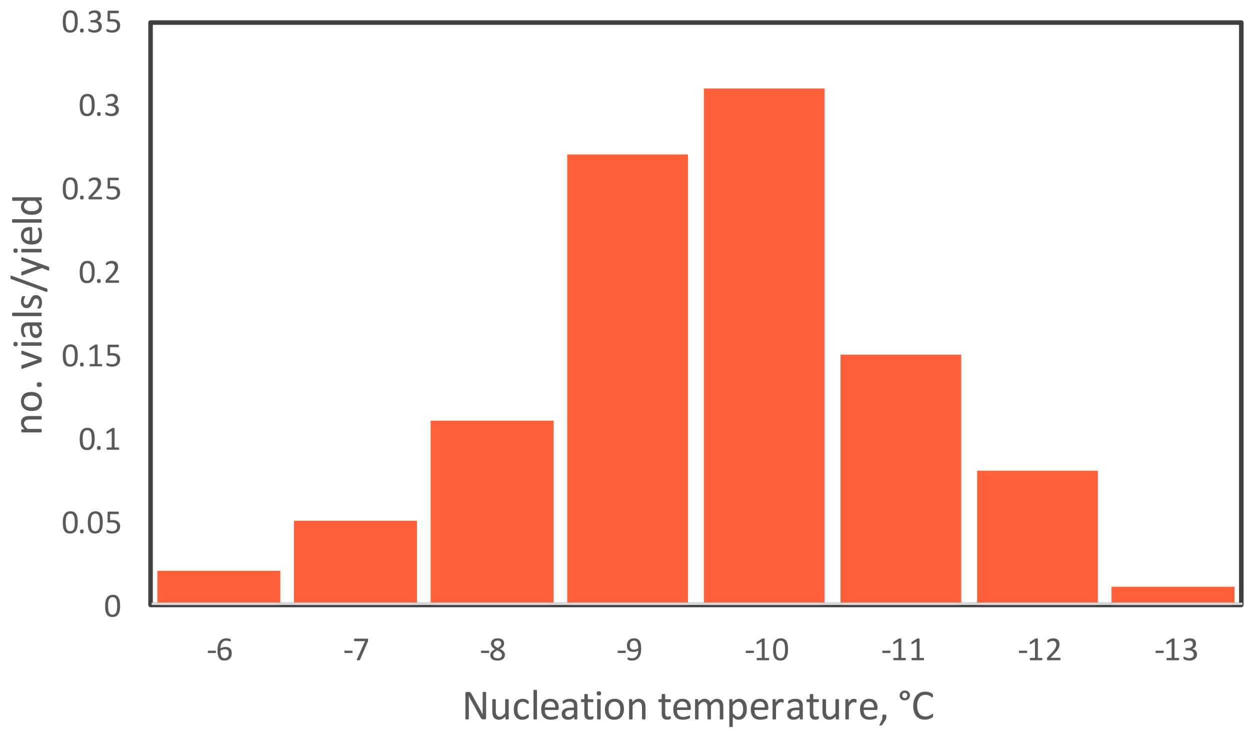
Present

Near future
>2020

Drawbacks of batch freeze-drying

Heterogeneity in freezing behavior …

- temperature of nucleation is not uniform within the batch of vials, but is stochastically distributed,



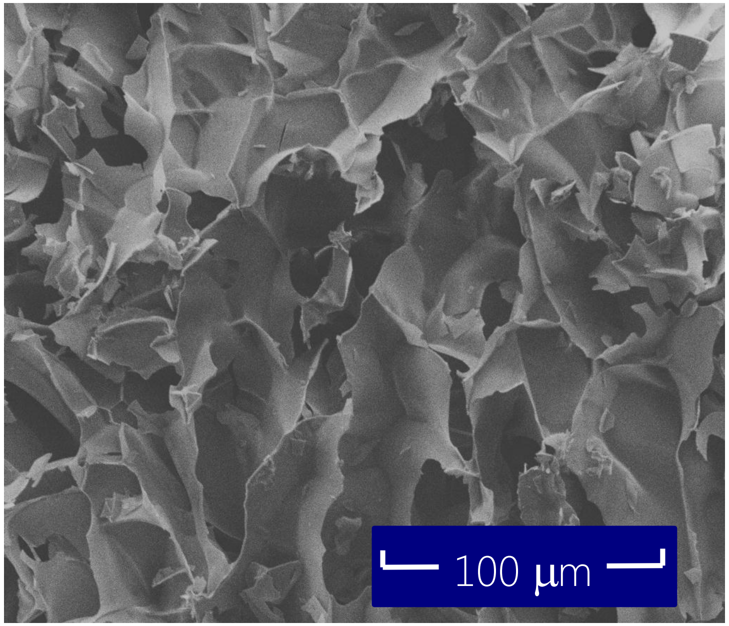
Distribution of the nucleation temperature as observed in a batch freeze-drying cycle

Drawbacks of batch freeze-drying

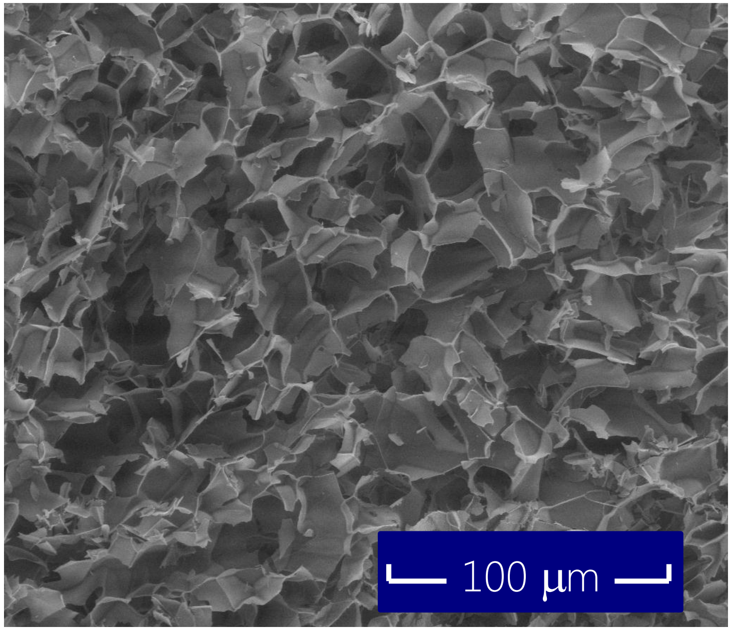
Heterogeneity in freezing behavior …

- temperature of nucleation is not uniform within the batch of vials, but is stochastically distributed
- ice structure and, hence, cake morphology changes from vial to vial

T_n = −10 °C



T_n = −15 °C



SEM micrographs of mannitol 5% as produced by batch freeze-drying

Drawbacks of batch freeze-drying

Heterogeneity in freezing behavior …

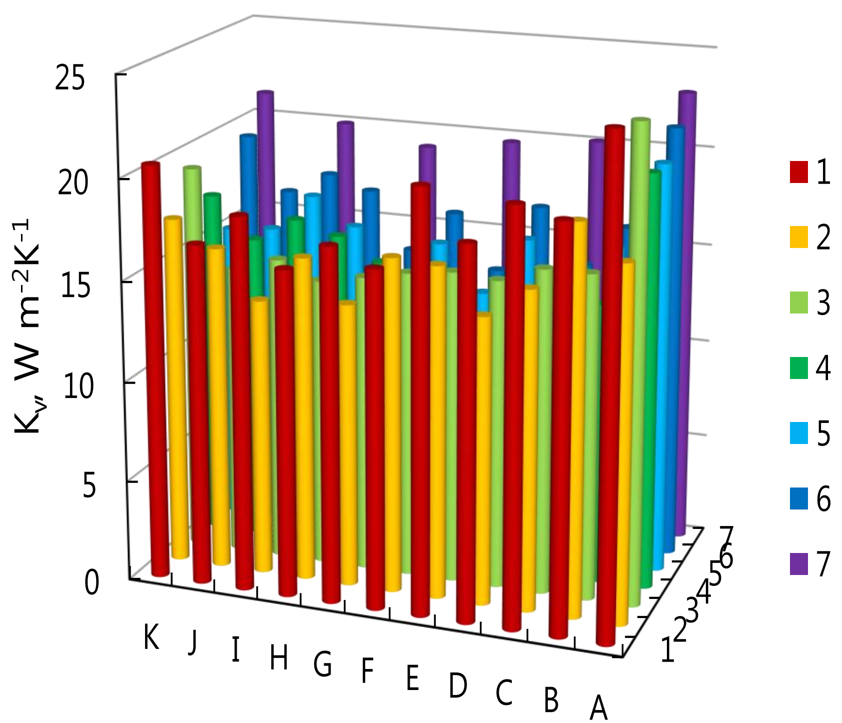
- temperature of nucleation is not uniform within the batch of vials, but is stochastically distributed
- ice structure and, hence, cake morphology changes from vial to vial
- both primary and secondary drying behavior change from vial to vial
- vial-to-vial variations in polymorphs composition
- large distributions in residual moisture and potentially in API activity/stability

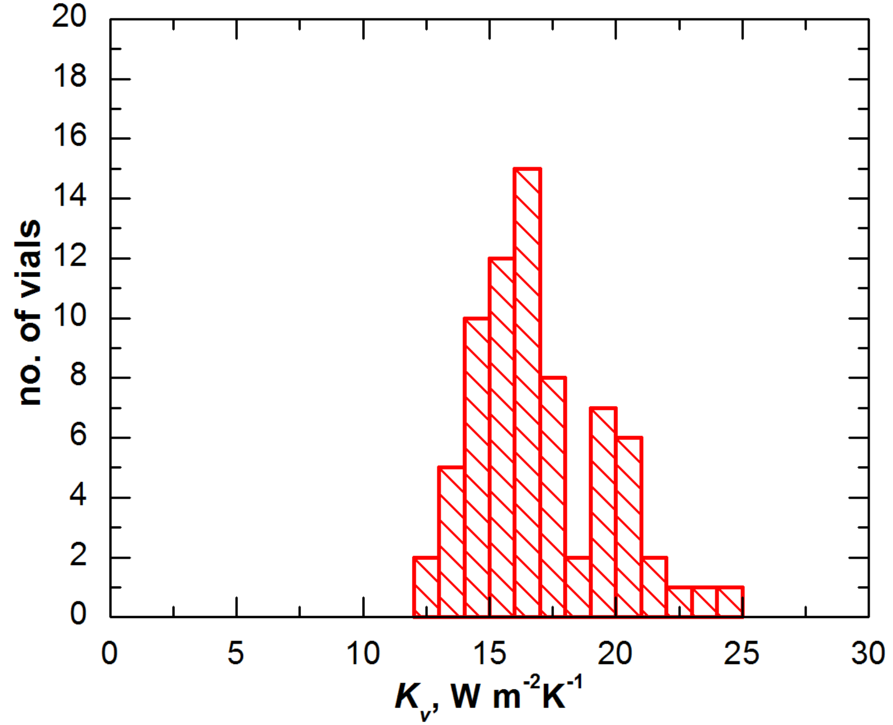
Continuous freeze-drying might be beneficial to …

- achieve a narrow distribution in nucleation temperature
- make the frozen product morphology more uniform
- make drying behavior more uniform among the vials of the batch
- reduce vial-to-vial heterogeneity

Drawbacks of batch freeze-drying

Heterogeneity in heat transfer ...

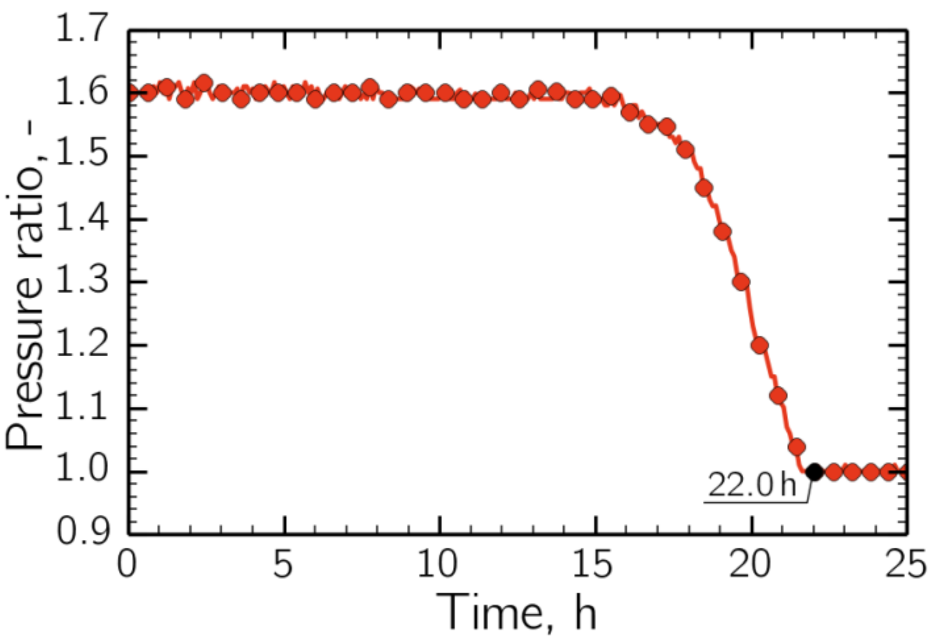




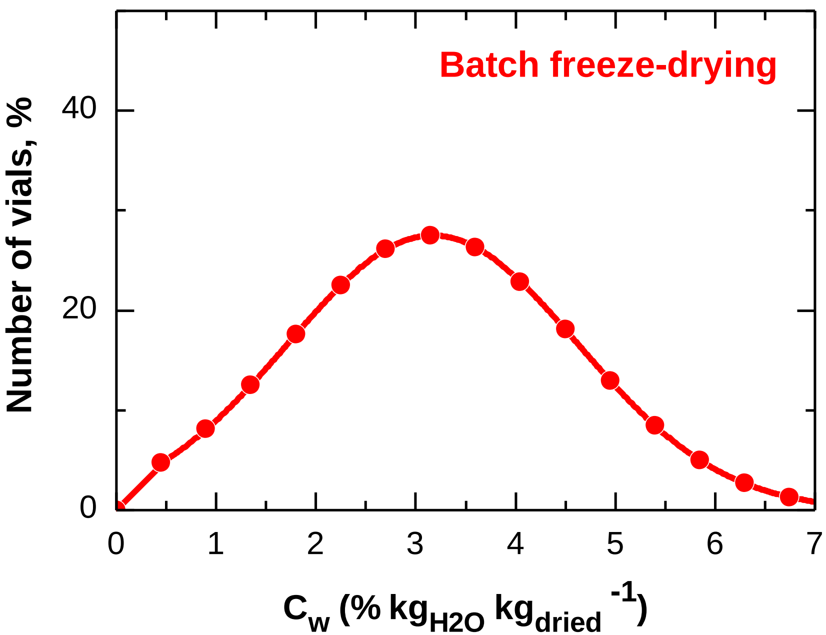
Spatial and statistical distribution of the heat transfer coefficient, between shelf and container, within a batch of vials. Data refer to primary drying, 10 Pa as chamber pressure

Drawbacks of batch freeze-drying

Heterogeneity in heat transfer …



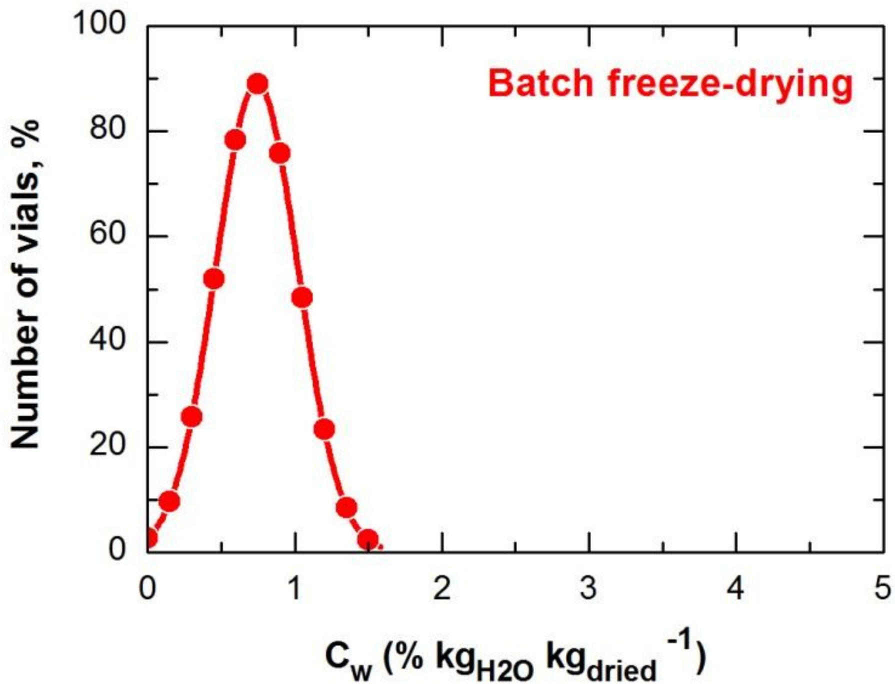
Evolution of pressure ratio as observed in a batch freeze-dryer



Statistical distribution of the residual moisture within the lyophilized samples at the end of primary drying

Drawbacks of batch freeze-drying

- Variations in product morphology due to freezing
- Variations in the residual moisture at the end of primary drying
- Variations in the residual moisture at the end of secondary drying



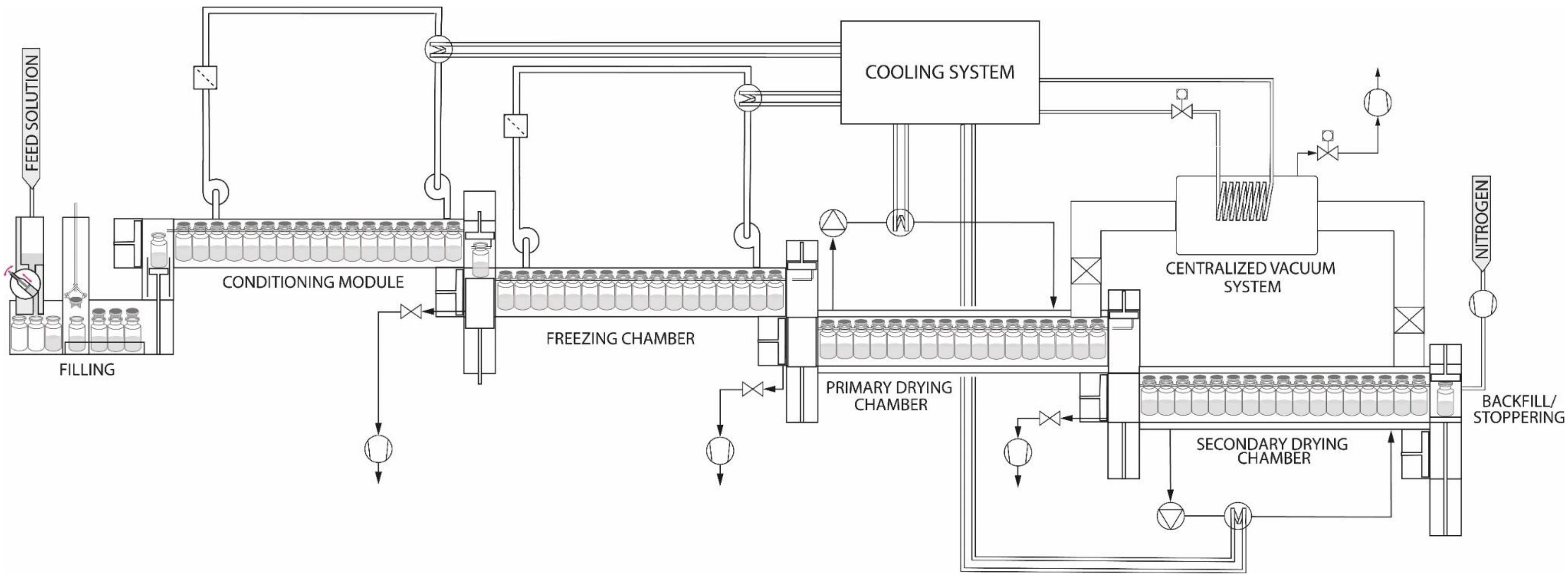
Statistical distribution of residual moisture within the lyophilized samples as observed at the end of secondary drying

The extent of heterogeneity in freezing and drying behavior is equipment-specific.

A cycle developed in a laboratory freeze-dryer cannot be transferred without modifications to the production unit → scale up

A new concept for the continuous freeze-drying of unit doses

<u>OBJECTIVE</u>: development of a continuous freeze-dryer that produces a final product having similar properties and structures to that obtained by a conventional batch unit.

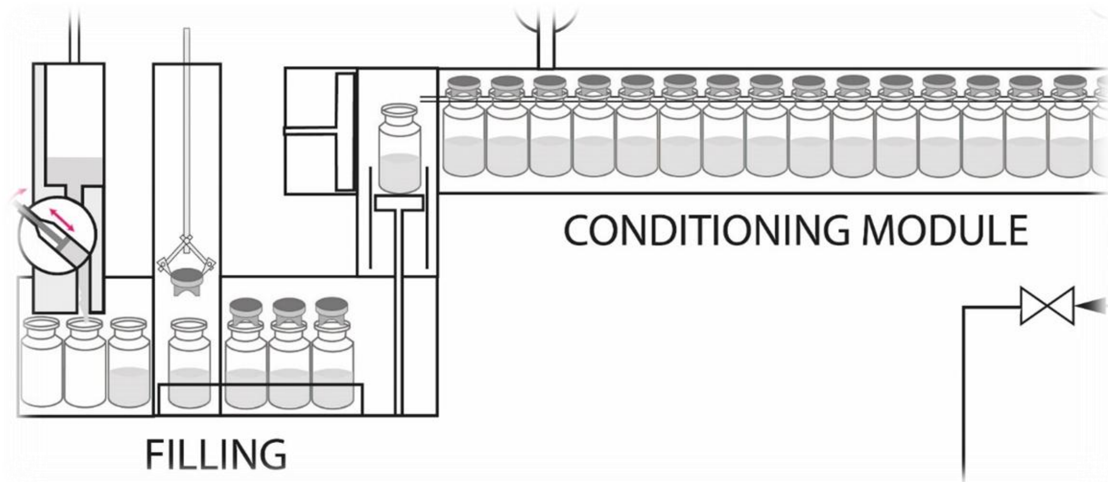


FILLING → CONDITION-ING → VACUUM CHAMBER → PRIMARY DRYING MODULE → SECONDARY DRYING MODULE → BACK/STOPPERING

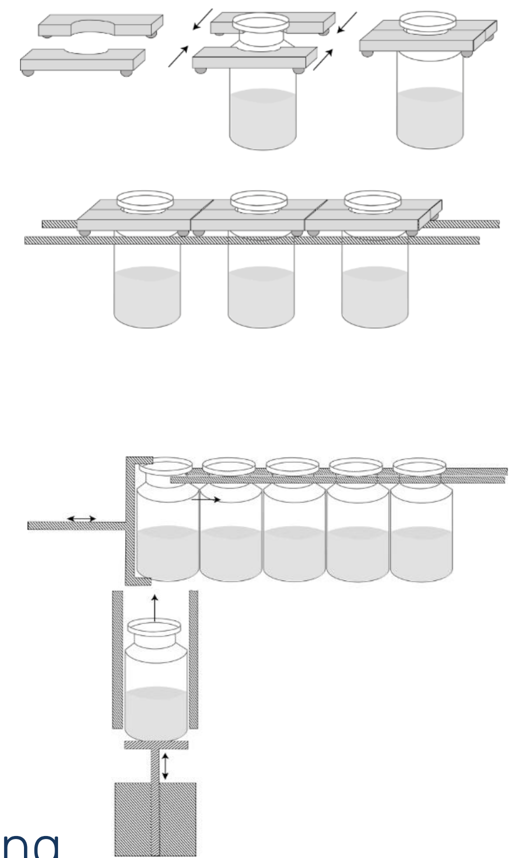
A new concept for the continuous freeze-drying of unit doses

Filling and Loading

Conditioning module
Nucleation module
Freezing module
Primary drying module
Secondary drying module



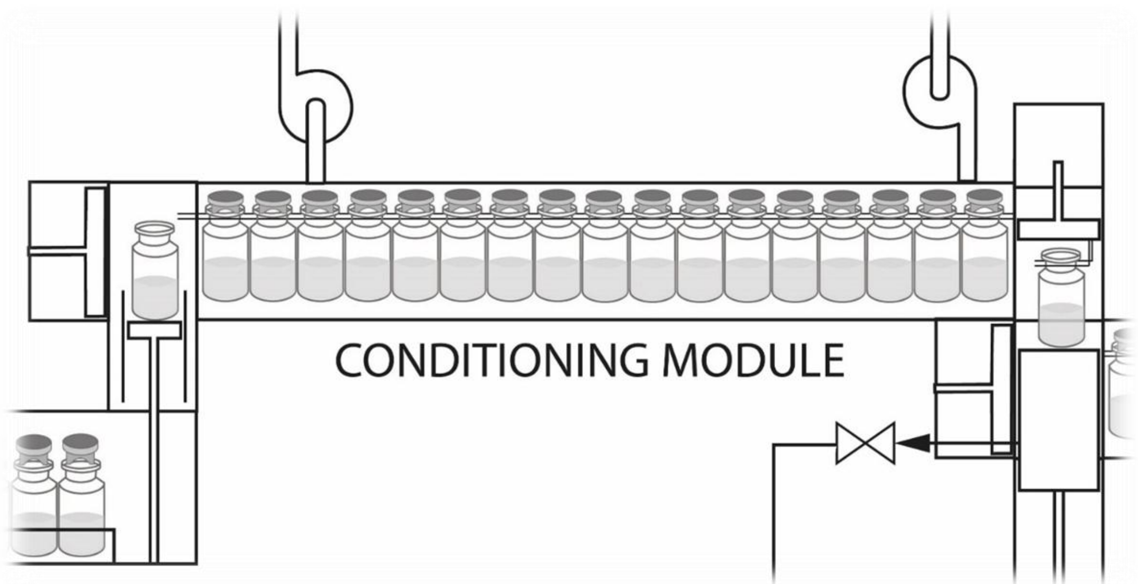
Moving of vials



The continuous flow of vials is achieved by suspending the vials over a track → uniformity in heat transfer

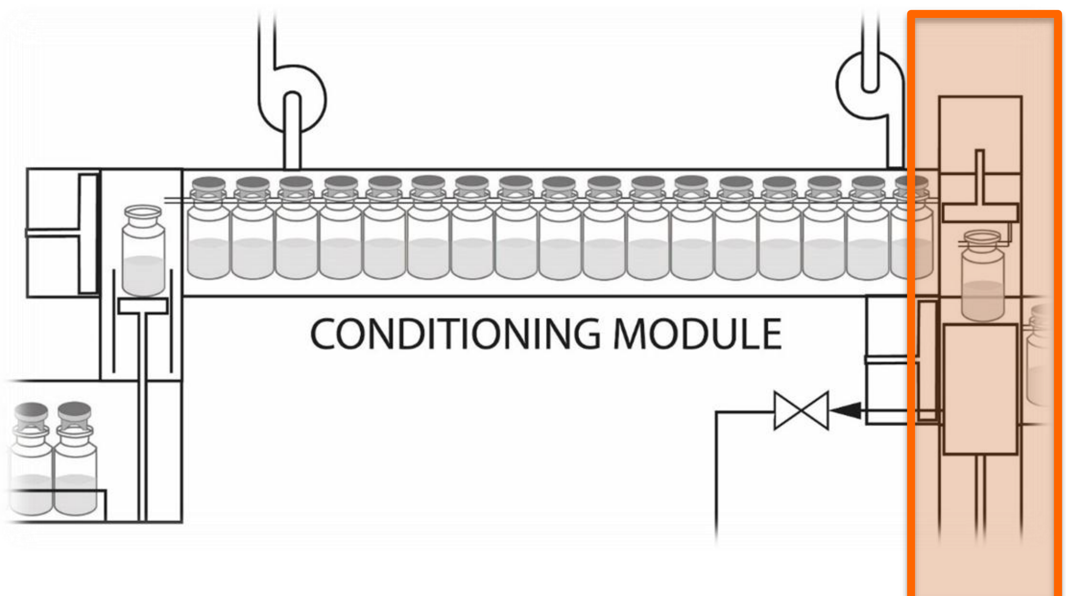
A new concept for the continuous freeze-drying of unit doses

- Filling and Loading
- **Conditioning module**
- Nucleation module
- Freezing module
- Primary drying module
- Secondary drying module

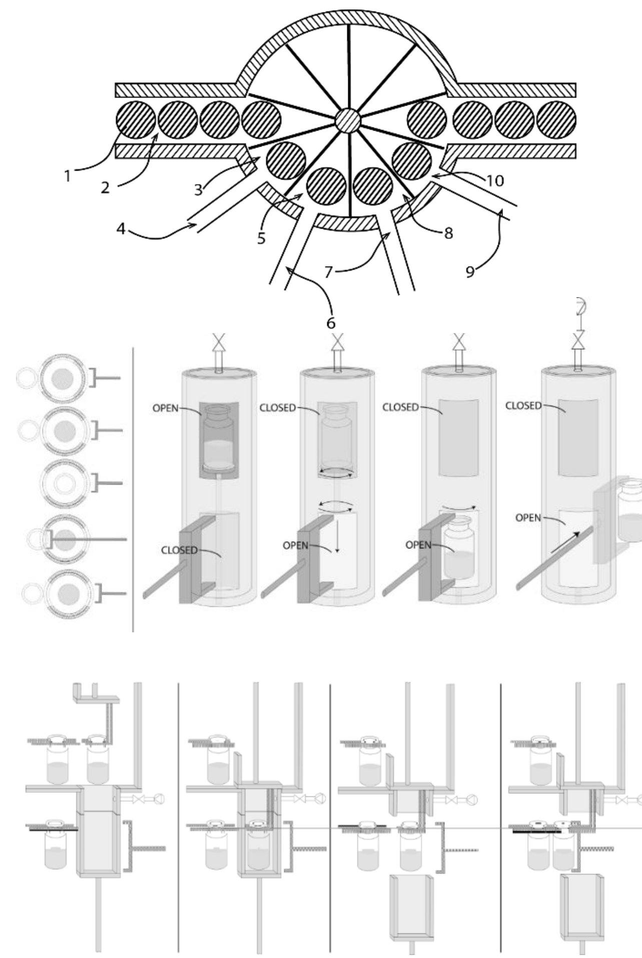


A new concept for the continuous freeze-drying of unit doses

Filling and Loading
Conditioning module
Nucleation module
Freezing module
Primary drying module
Secondary drying module

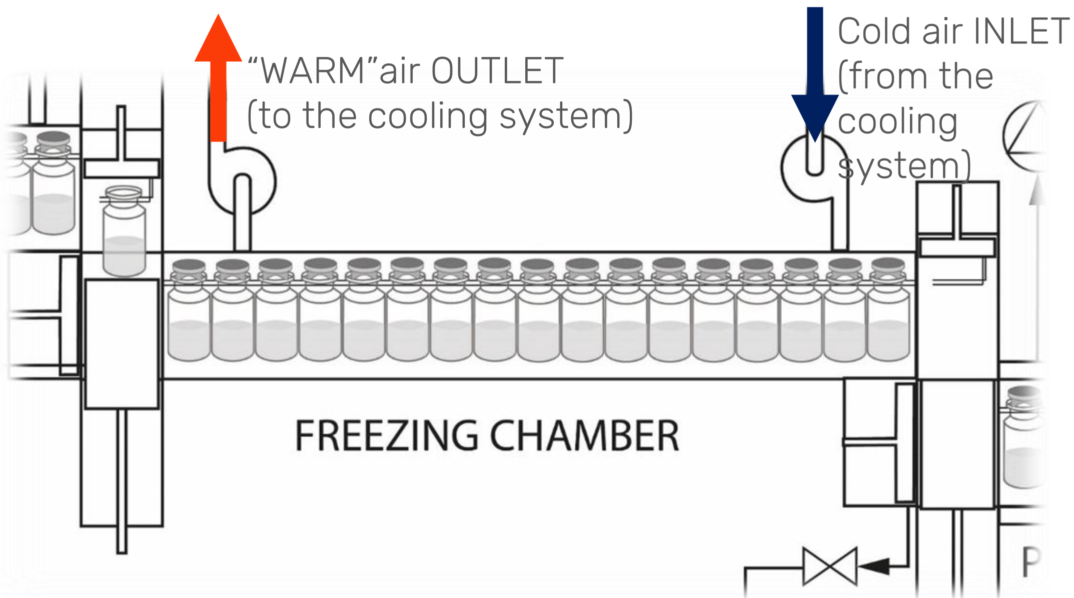


Example of nucleation chambers



A new concept for the continuous freeze-drying of unit doses

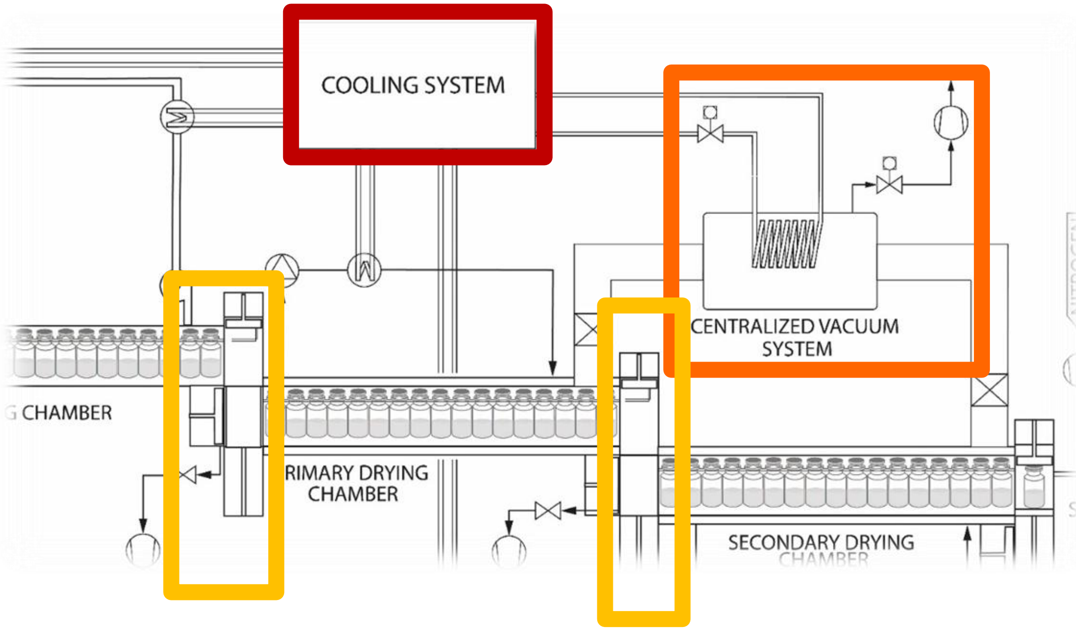
Filling and Loading
Conditioning module
Nucleation module
Freezing module
Primary drying module
Secondary drying module



- The nucleated solution is further cooled by forced convection until the its complete solidification.
- The external surface of the vessel is equally flushed by the cryogenic gas.
- Different freezing protocols can be performed modulating temperature and velocity of cryogenic gas.

A new concept for the continuous freeze-drying of unit doses

Filling and Loading
Conditioning module
Nucleation module
Freezing module
Primary drying module
Secondary drying module



In the primary drying module …

- Vials are exposed to low temperature and pressure
- Heat is transferred by radiation from temperature-controlled surfaces

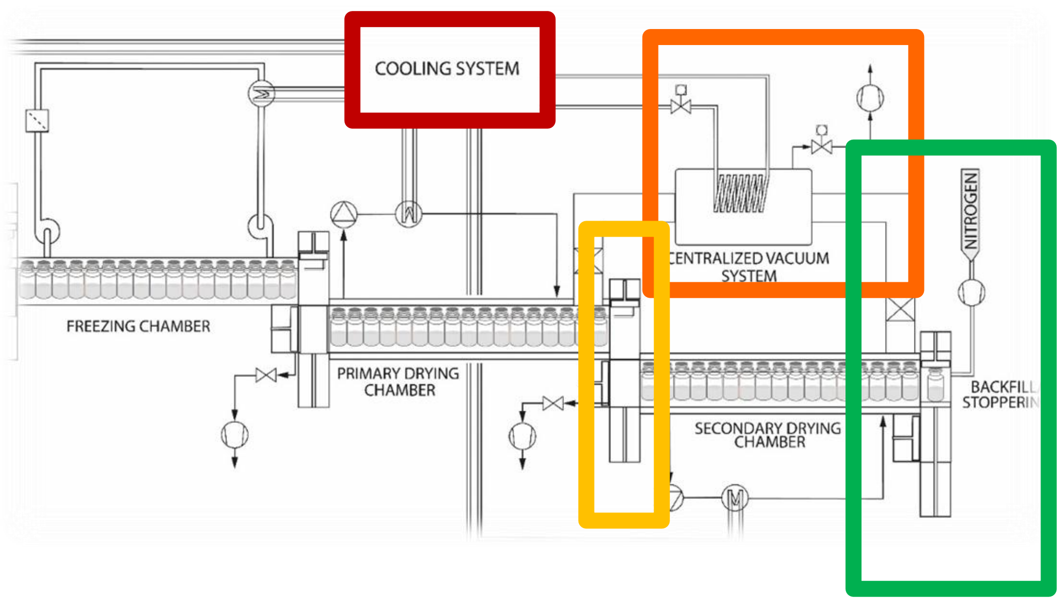
Vacuum system (condenser + vacuum pump)
Cooling/heating system
Sluice-gate/load-lock

A new concept for the continuous freeze-drying of unit doses

Filling and Loading
Conditioning module
Nucleation module
Freezing module
Primary drying
Secondary drying module

In the secondary drying module …

- Vials are exposed to high temperature and low pressure so as to promote desorption of bounded water

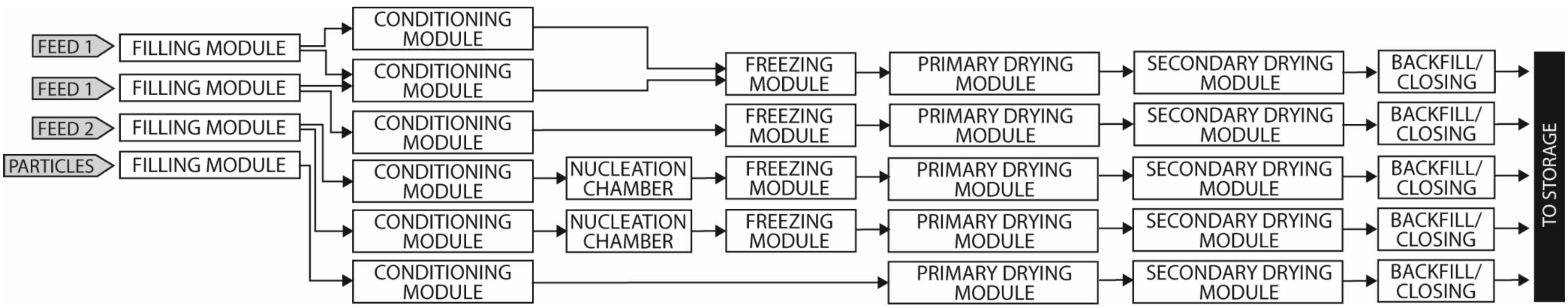


Vacuum system (condenser + vacuum pump)
Cooling/heating system
Sluice-gate/load-lock
Stoppering/sealing

A new concept for the continuous freeze-drying of unit doses

Flexibility & Modularity

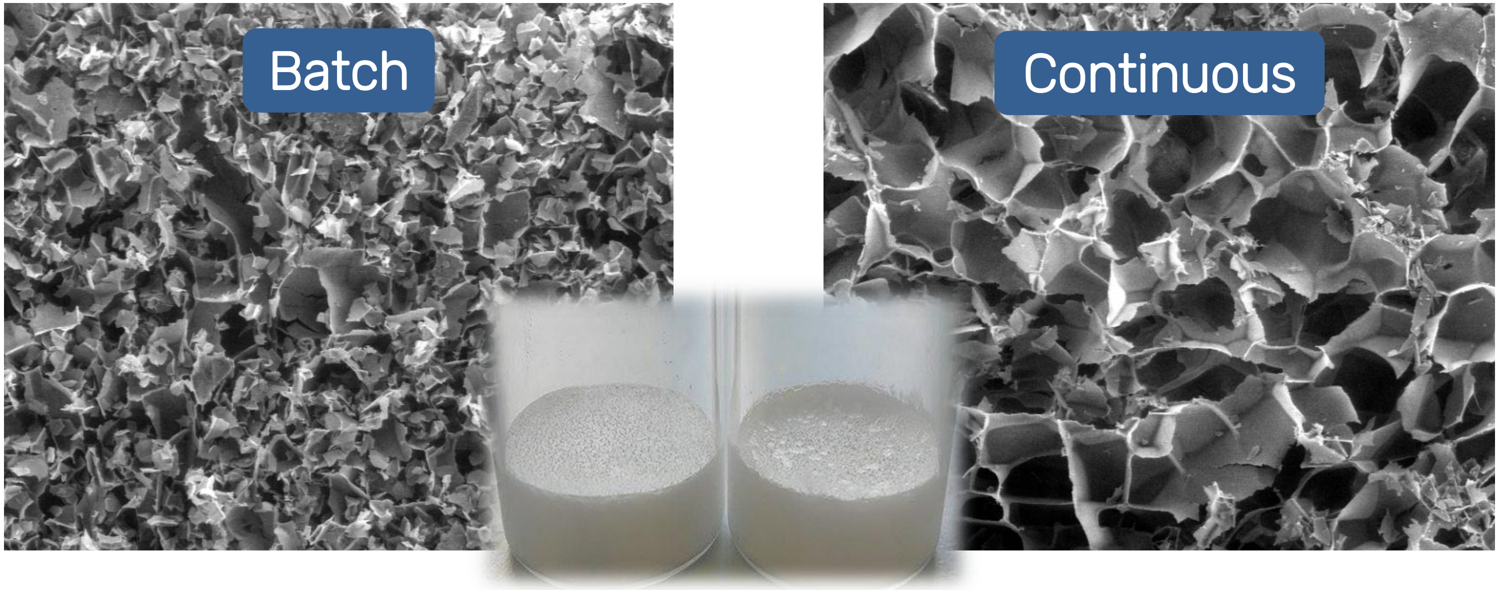
- The various modules can be combined to make the system more flexible and treating products from different upstream feeds.



Experimental results

Product morphology

- More precise control of freezing conditions
- Larger pores and hence smaller resistance to mass transfer during primary drying

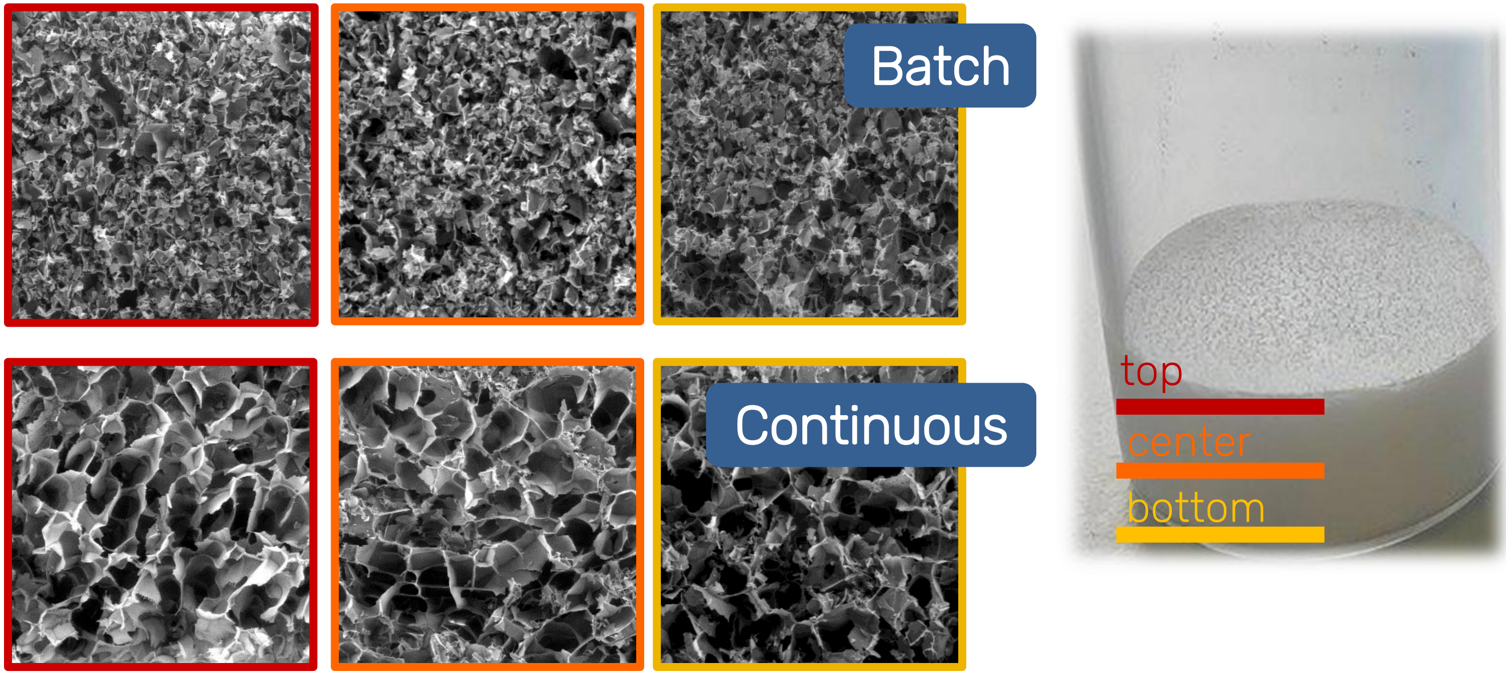


SEM images of lyophilized mannitol samples produced on constant drying conditions. Images refer to the same enlargement

Experimental results

Product morphology

- More precise control of freezing conditions
- Larger pores and hence smaller resistance to mass transfer during primary drying
- Intra-vial heterogeneity is less evident



SEM images of lyophilized mannitol samples

Experimental results

Process performances

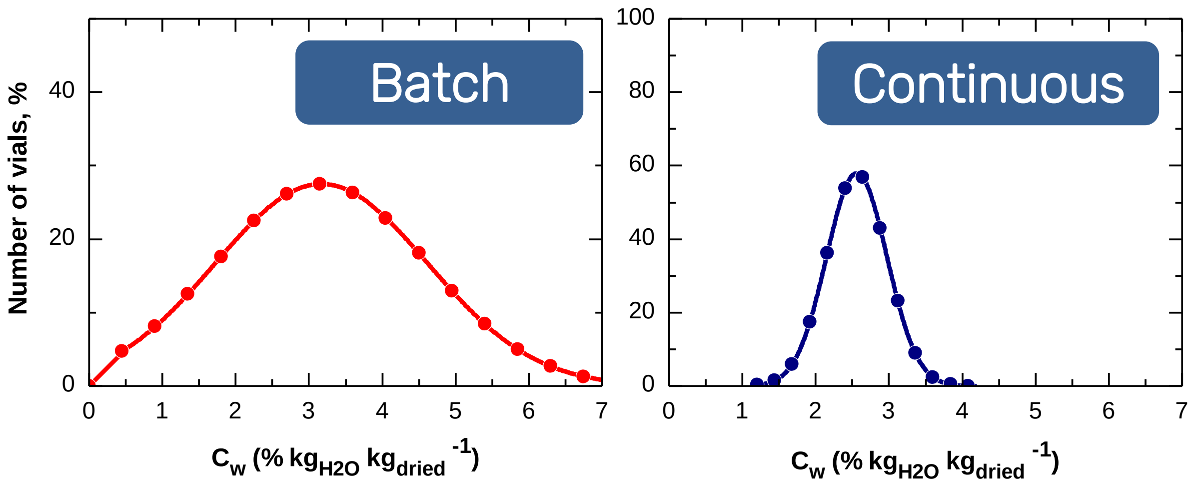
- Larger pores and hence shorter primary drying
- Breaks of a typical batch production can be 20% to 50% of the total cycle time
- The overall cycle time is up to 5 times shorter

	Loading	Leak test	Freezing	Primary drying	Soak time	Secondary drying	Closing	Unloading	Defrost/CIP /SIP/H202
Batch	✓ 5 h	✓ 2-3 h	✓ 6 h	✓ LONG	✓ 6 h	✓ SHORT	✓ 1 h	✓ 6 h	✓ 6 h
Continuous			✓ < 1 h	✓ SHORTER		✓ SHORT			

Experimental results

Process performances

- Larger pores and hence shorter primary drying
- Breaks of a typical batch production can be 20% to 50% of the total cycle time
- The overall cycle time is up to 5 times shorter
- Distribution of the residual moisture at the end of drying is more uniform

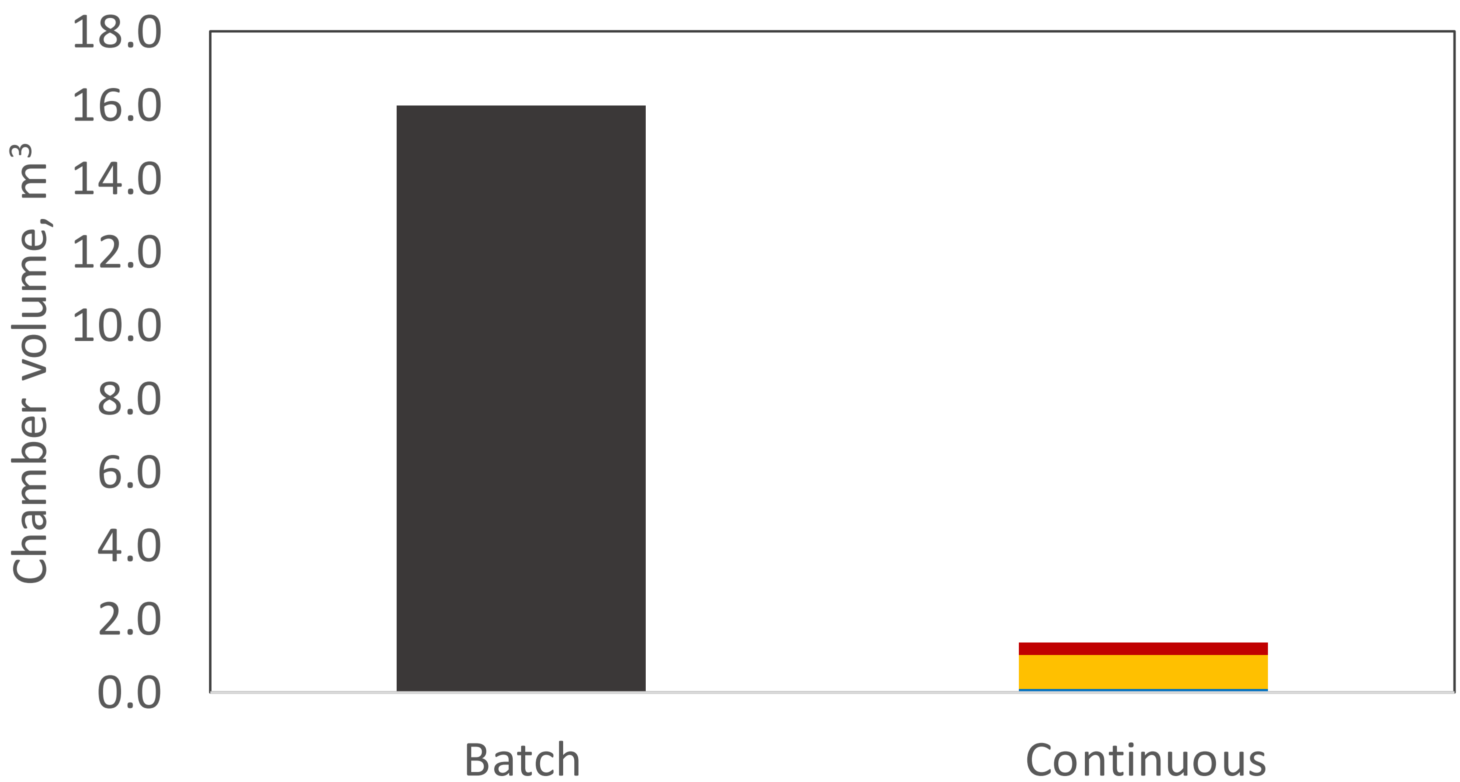


Distribution of the final residual moisture for a sucrose-based formulation (250 vials)

Experimental results

- Case study #1 – 100,000 vials/week

The equipment volume is approx. 15 times smaller



Conclusions

Reduce the risk of product contamination

- No manual handling, increased safety
- The processing time is shorter

Modular and smaller equipment and facilities

- More flexible operation
- Reduced inventory
- Lower capital costs, less work-in-progress materials

Eliminate scale-up from lab to production units

Process flexibility

- Bulk vs. particle-based material
- Yield can be adjusted on market request

Improve product quality

- Uniformity of the lot of production
- In-line control of product quality

Acknowledgements

Politecnico di Torino

Department of Applied Science and Technology

- Andrea Arsiccio
- Fiora Artusio
- Marco Bazzano
- Luigi C. Capozzi

Massachusetts Institute of Technology

Department of Chemical Engineering

Prof. Bernhardt Trout

Thanks for your attention!