Spray-freeze drying: a possible substitute for classical lyophilisation

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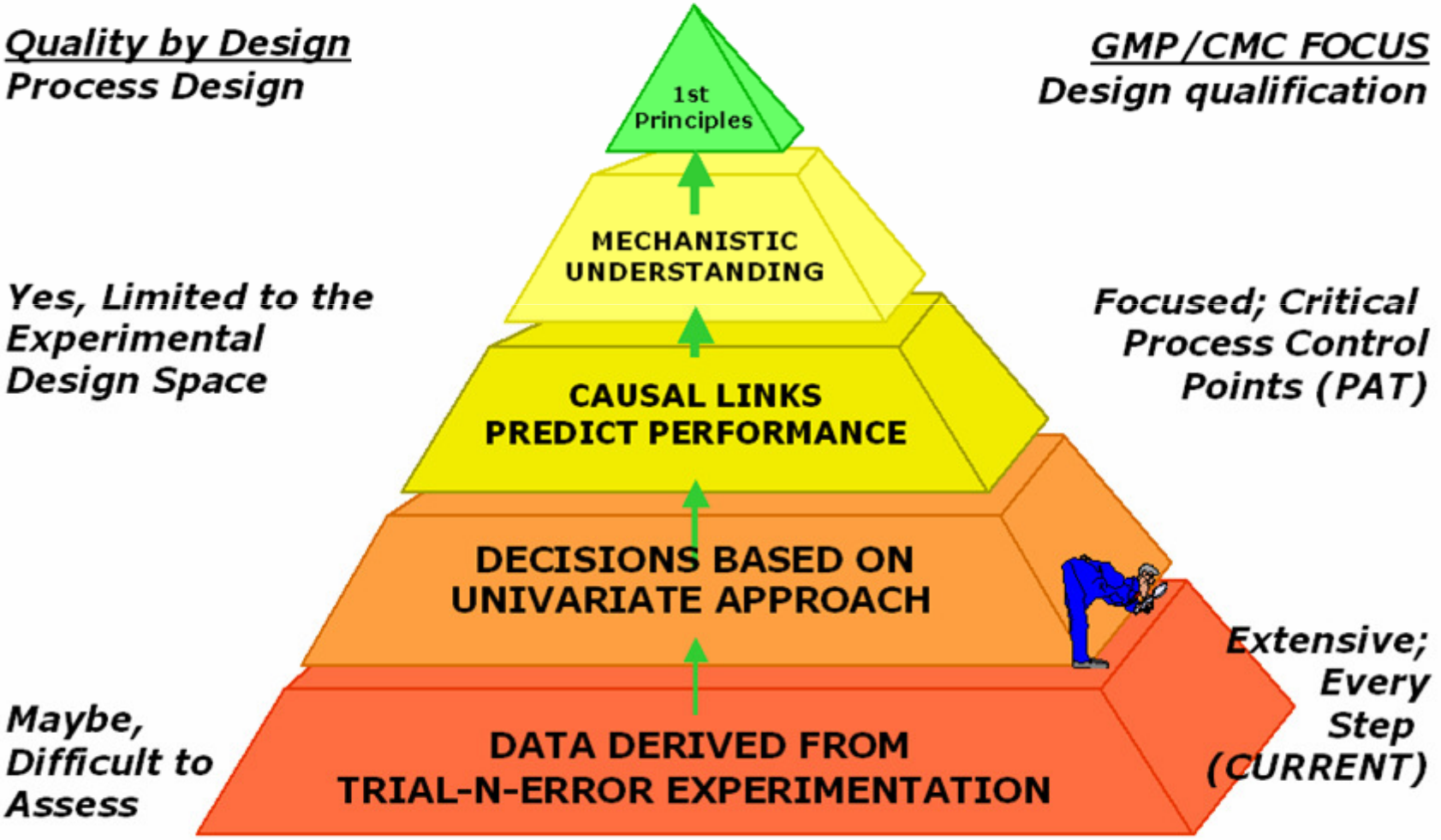
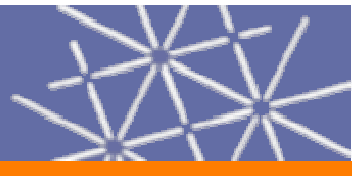
Product and Process Quality Knowledge: Science-Risk Based cGMP's



The SIGMA Concept I

FDA pushes forward the PAT Initiative for very good reasons:

- The variability of most pharmaceutical processes needs to be reduced.
- The performance of a process can be described by its Sigma value.



The SIGMA Concept II

- The champion is the chip industry with a six Sigma manufacturing performance (**static values**)
  - i.e. with an amount of defective samples ≤ 2 ppb.
- The performance of the pharmaceutical industry is around 2 Sigma (≤ 4.6 % defectives).

Identification of critical processes: Classical Lyophilisation

The major problem:

→ due to the extremly bad heat transfer the freezing and lyophilisation process of a solution filled in vials is in general problematic and lengthy, creating a batch to batch variability but also within a batch a variability from vial to vial.

→ Thus heat transfer is the limiting factor!

Historical Overview

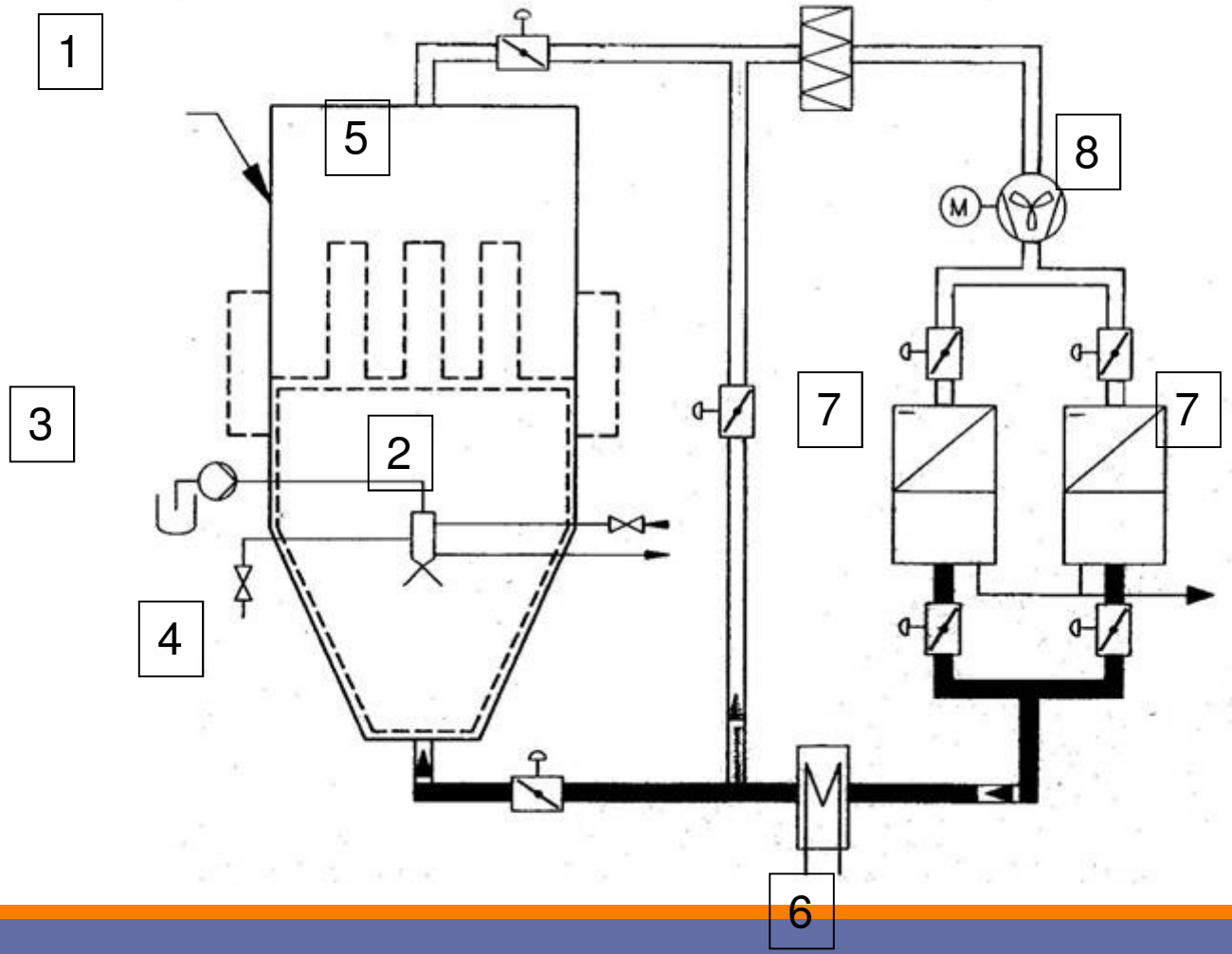
- Glatt started in the mid 80s together with University of Basel / Prof. Hans Leuenberger
- 4 research projects realized

Atmospheric Spray Freeze Drying

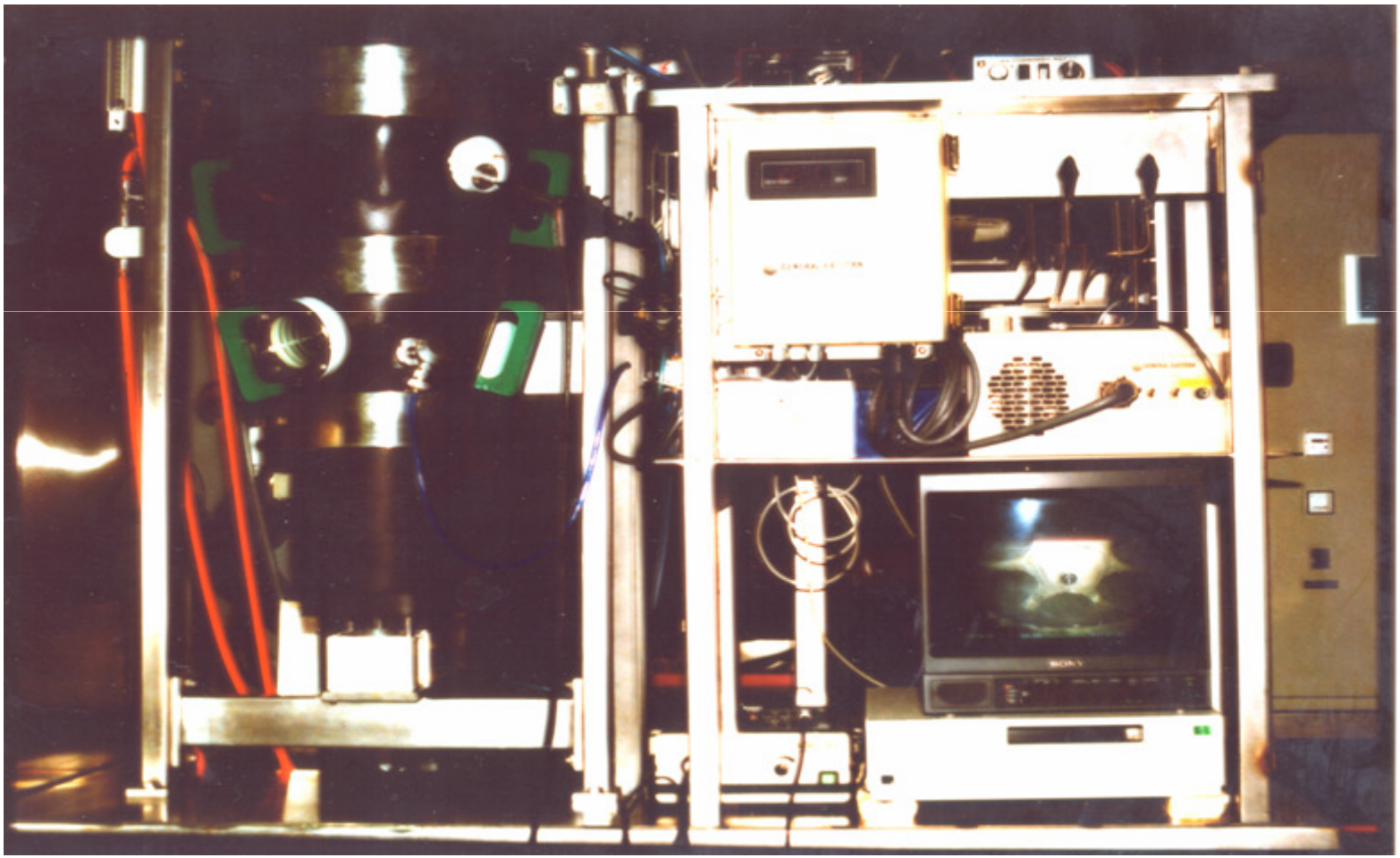
Expected Advantages
due to a better heat transfer:

- shorter drying times
- constant drying conditions
- free flowing particles, no cake
- Rapid dissolution properties

Spray freeze drying equipment



Design of the Closed Loop System

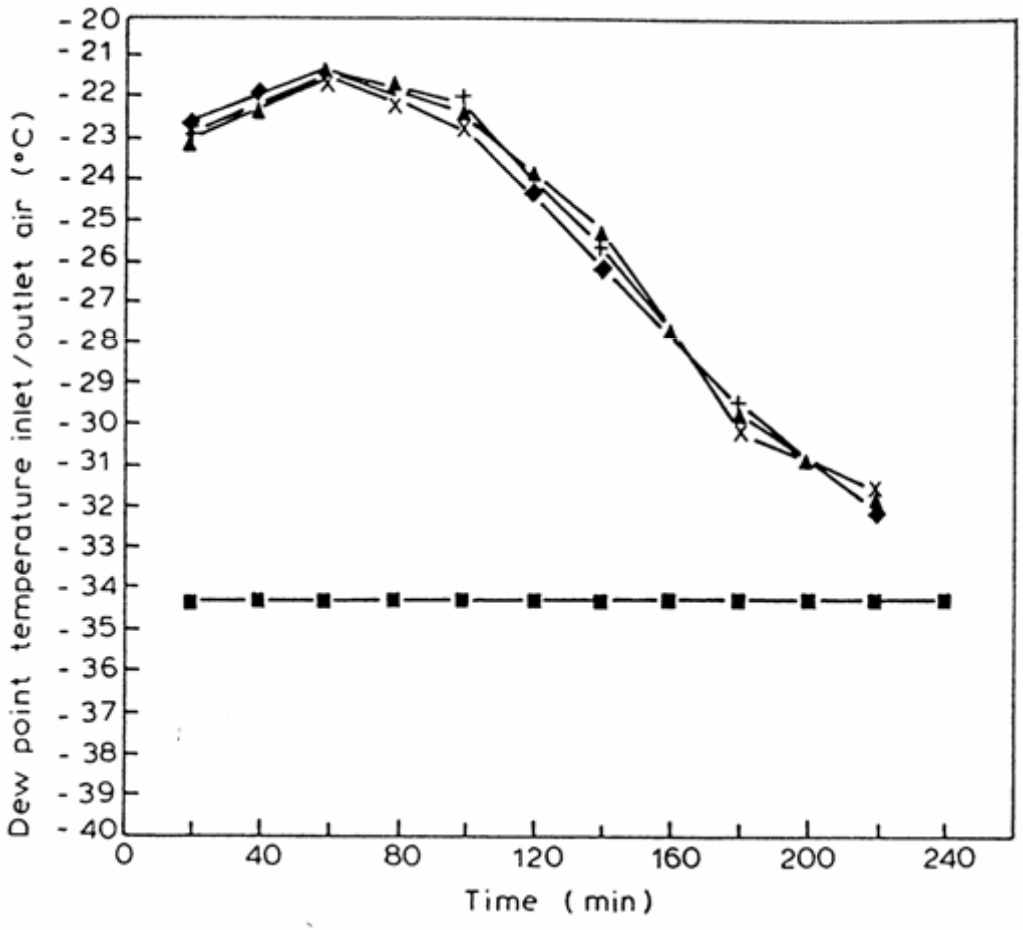


Spray freeze drying equipment

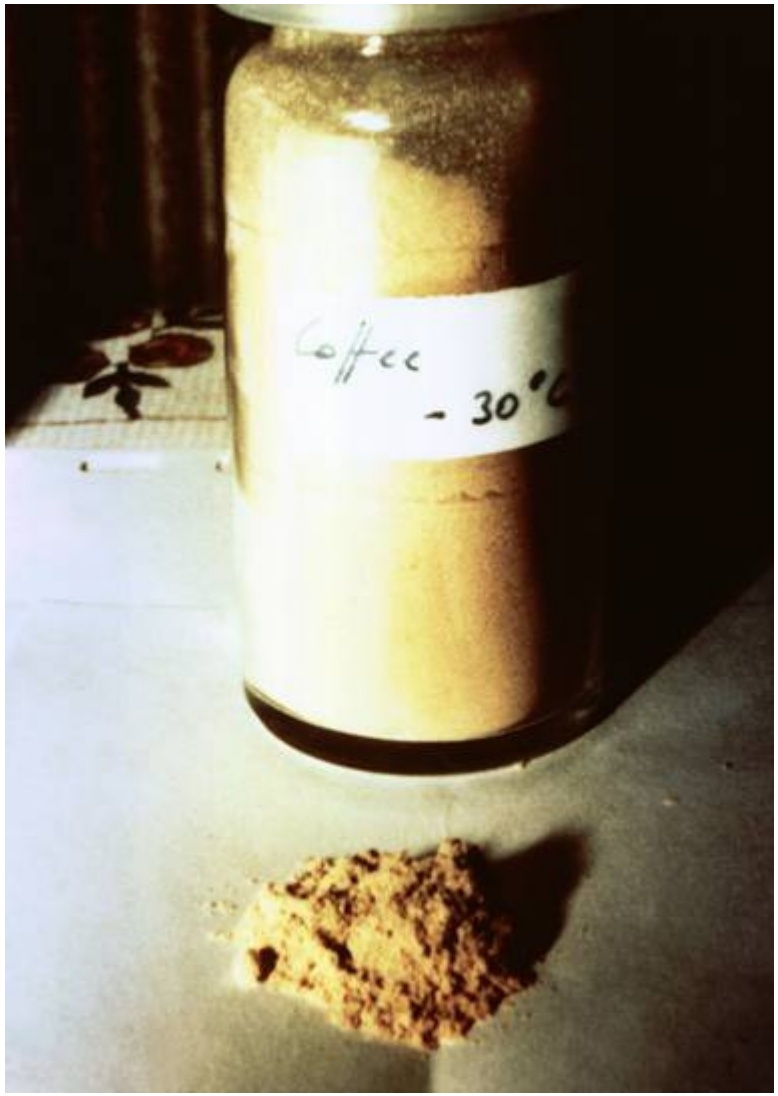
- product bowl: 5 l
- lowest inlet air temperature: - 60 °C
- heated nozzle (40 - 70 °C), height adjustable
- 2 condensers for alternate defrosting and freezing out of air humidity
- bypass to maintain low temperatur in equipment and for inlet air regulation

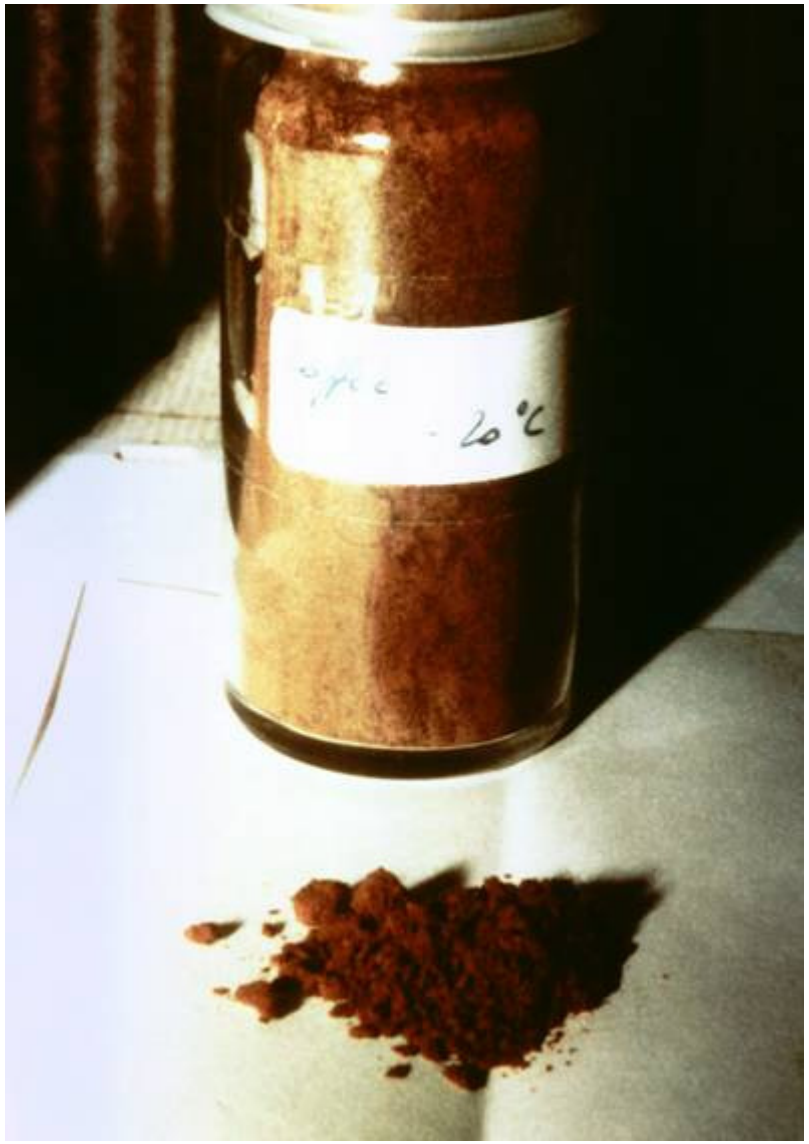
Design of the Closed Loop System

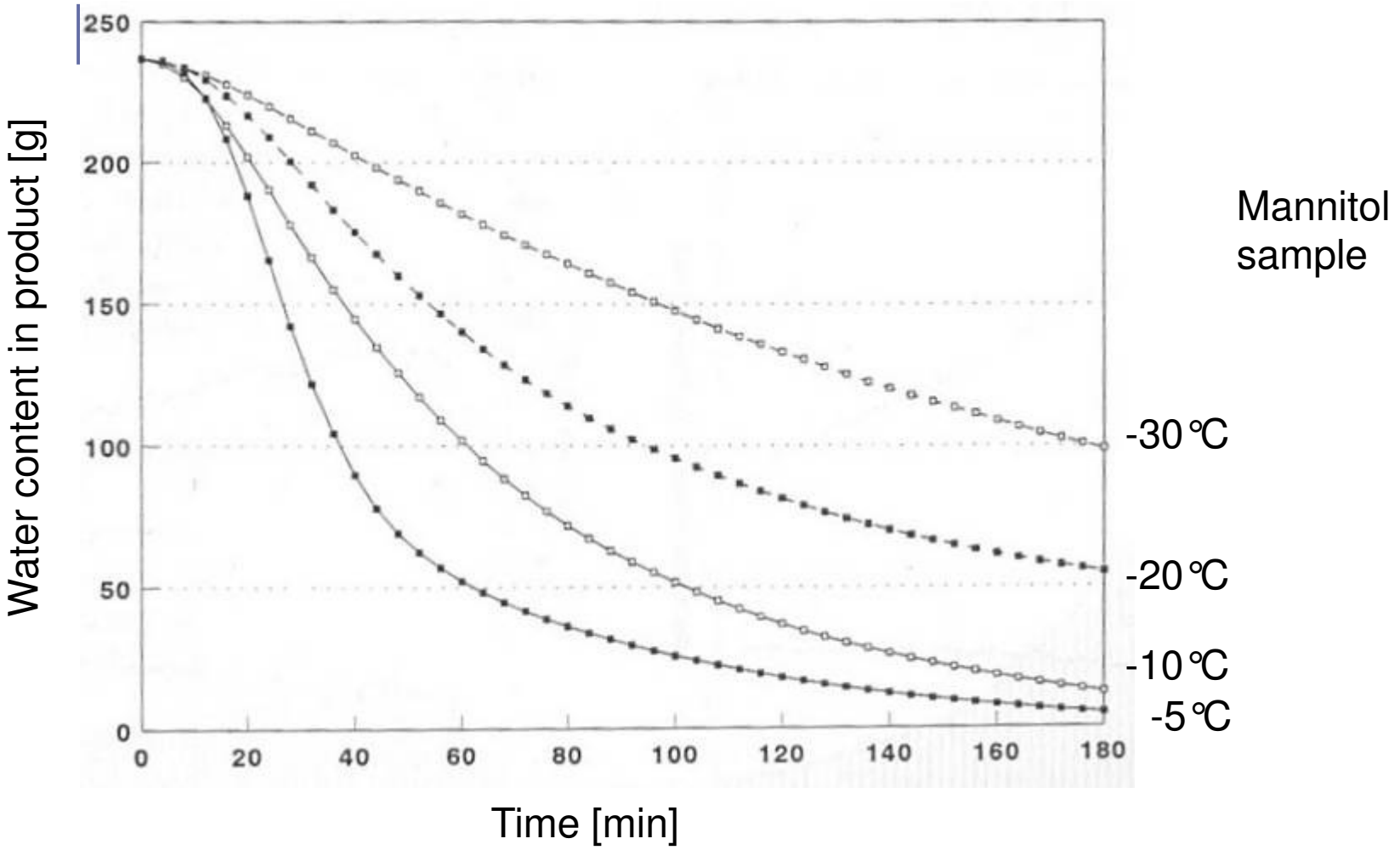
Dew Point Temperature Measurement of the **Inlet- and Outlet Air:**
Thus the kinetics of the
Lyophilisation can be controlled in real time!



Nescafé Gold
dissolved and
spray freeze dryed at
minus 30°C
retaining the flavors





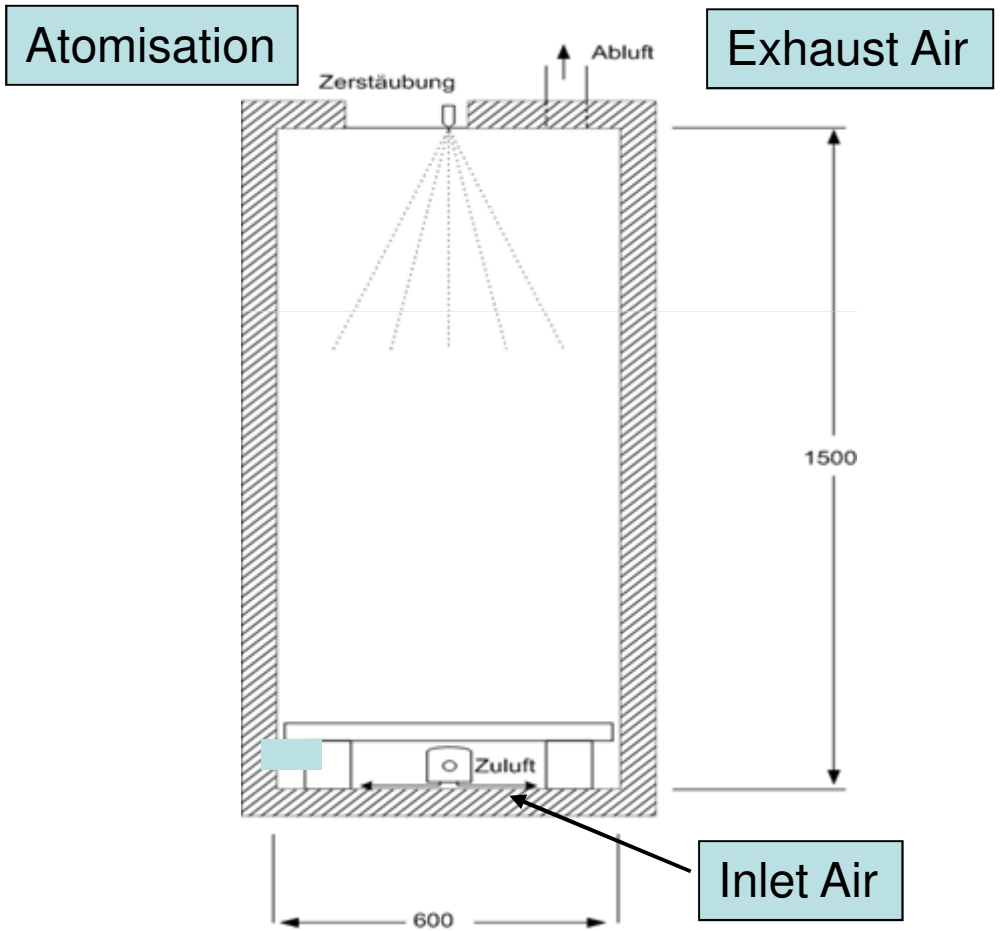


Mannitol sample

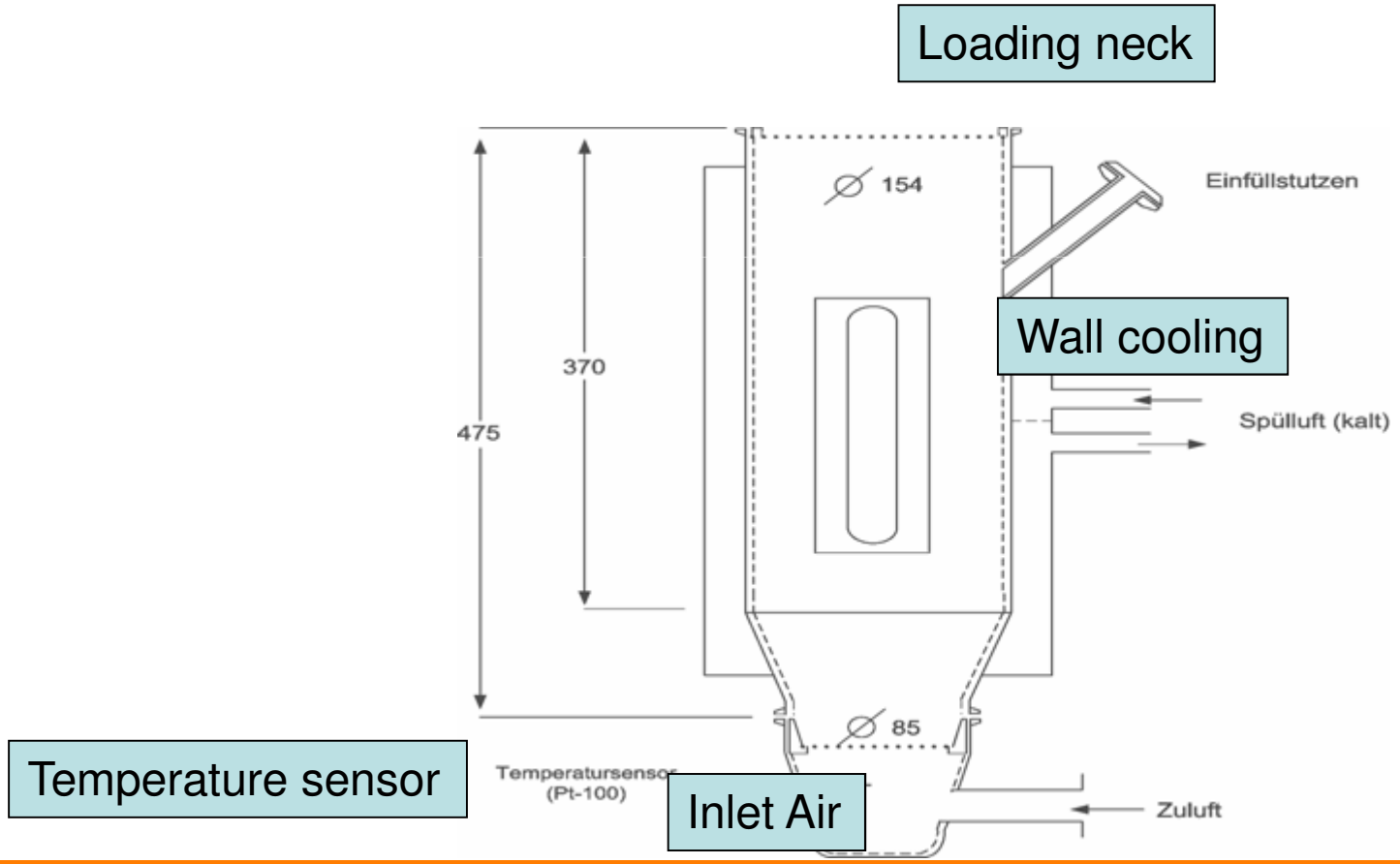
Results

- spray freeze drying possible
- fast drying compared to classical freeze drying
- „filter cake drying“ due to extreme freezing conditions with high air flow only (max. 10mm = 2 kg)

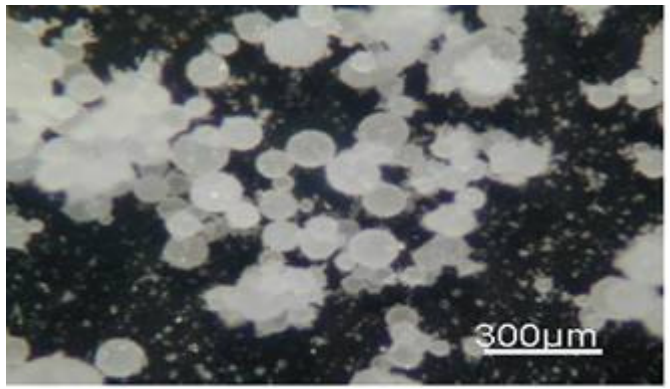
Process separation – Freezing step



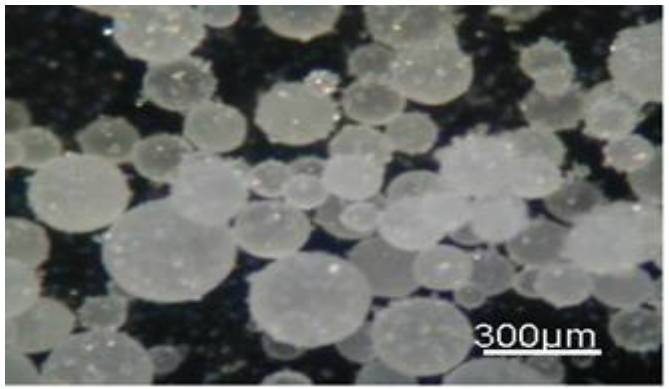
Process separation – Drying step



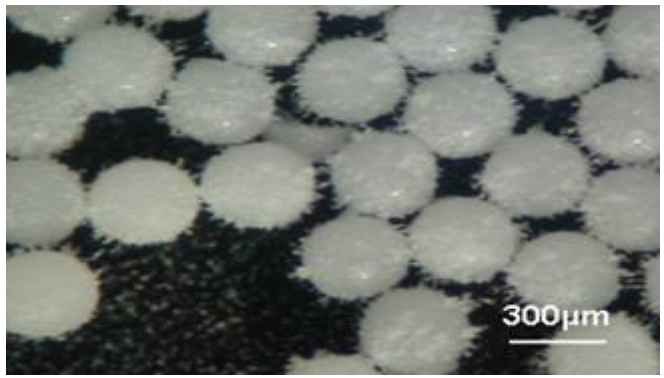
Spray Freezing



1. Ultrasonic nozzle

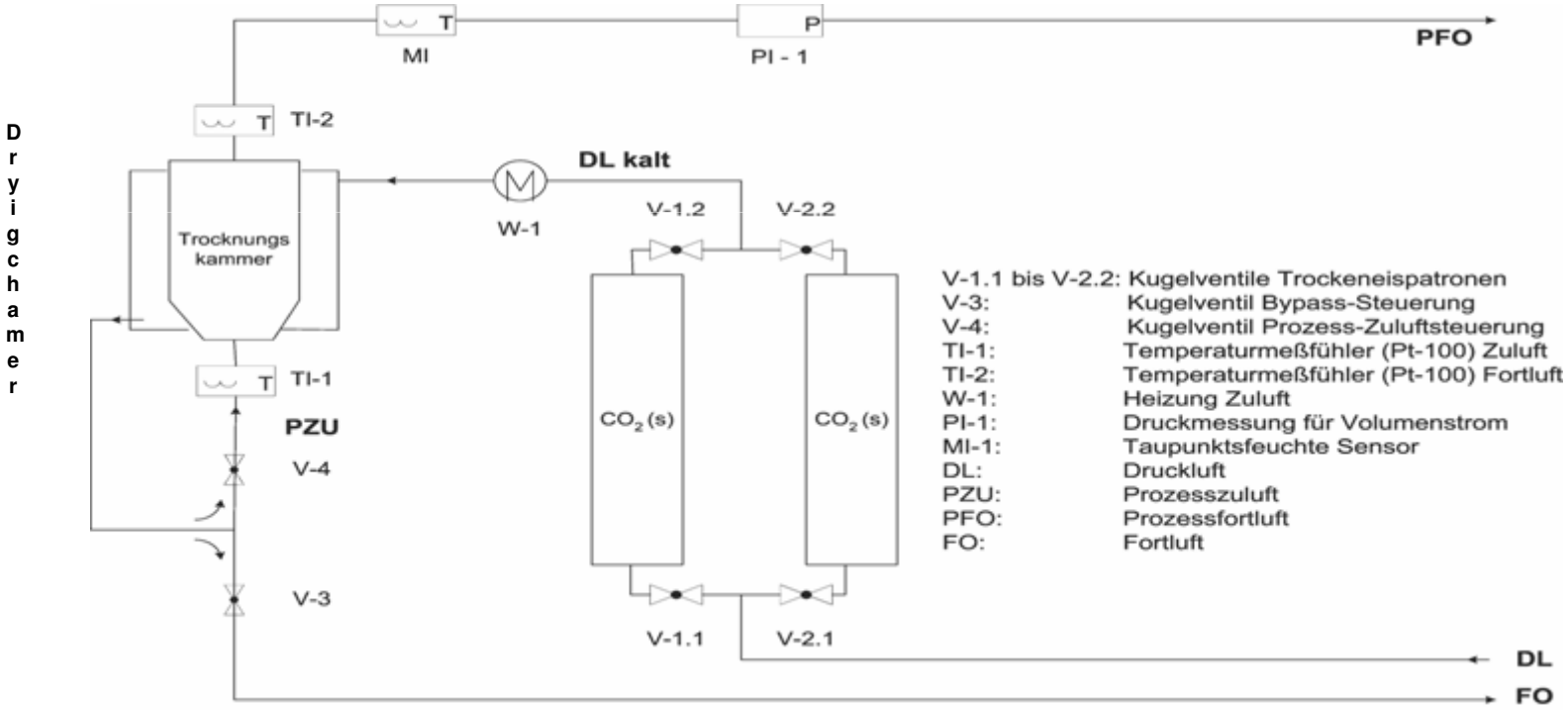


2. Binary nozzle



3. Prilling nozzle

Flow chart of drying equipment



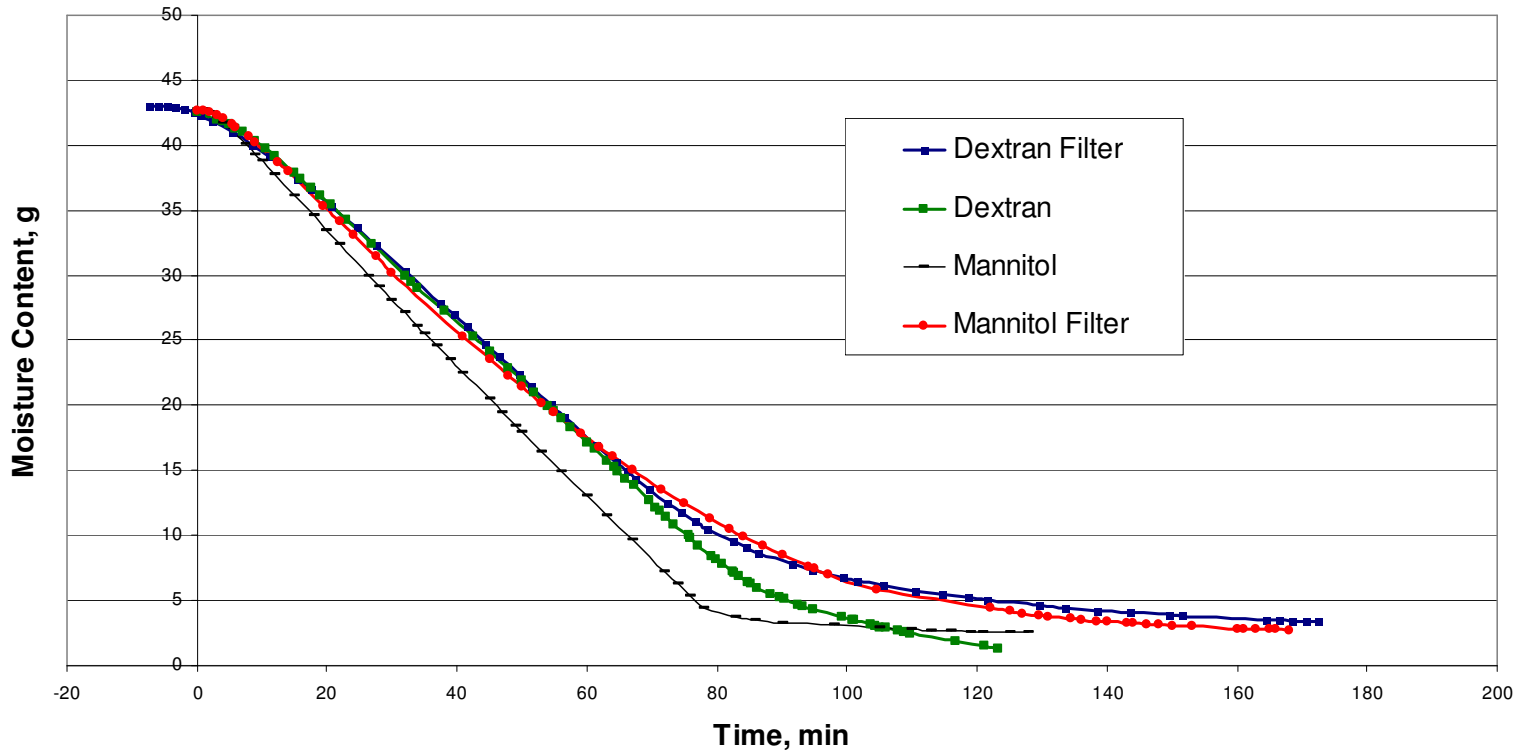
Drying

- Solution: 10% Trehalose
- Drying temperature: -32,5°C
- Batch size: 30 g frozen product

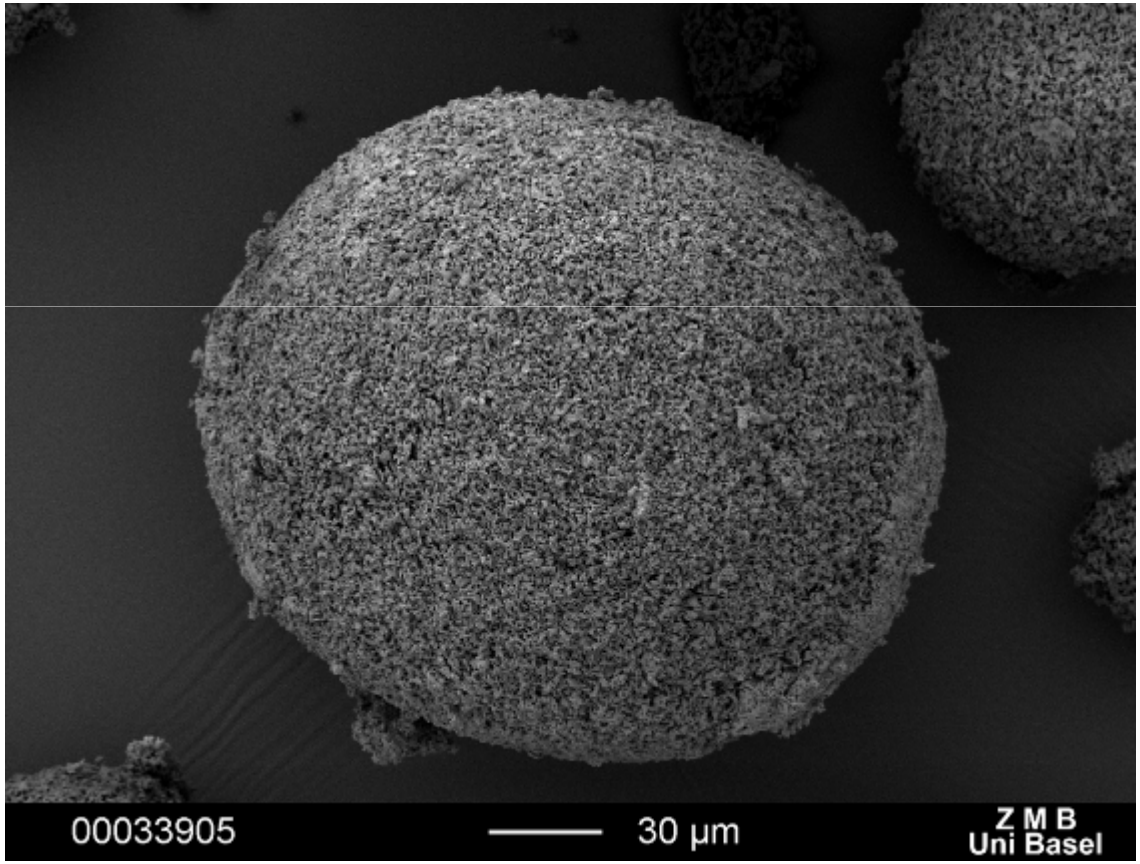
Parameters influencing drying speed

- Saturation of drying air // Air speed for fluidisation
- Surface of particles
- Length of pores // heat conduction of dried product layer
- Porosity
- Temperature

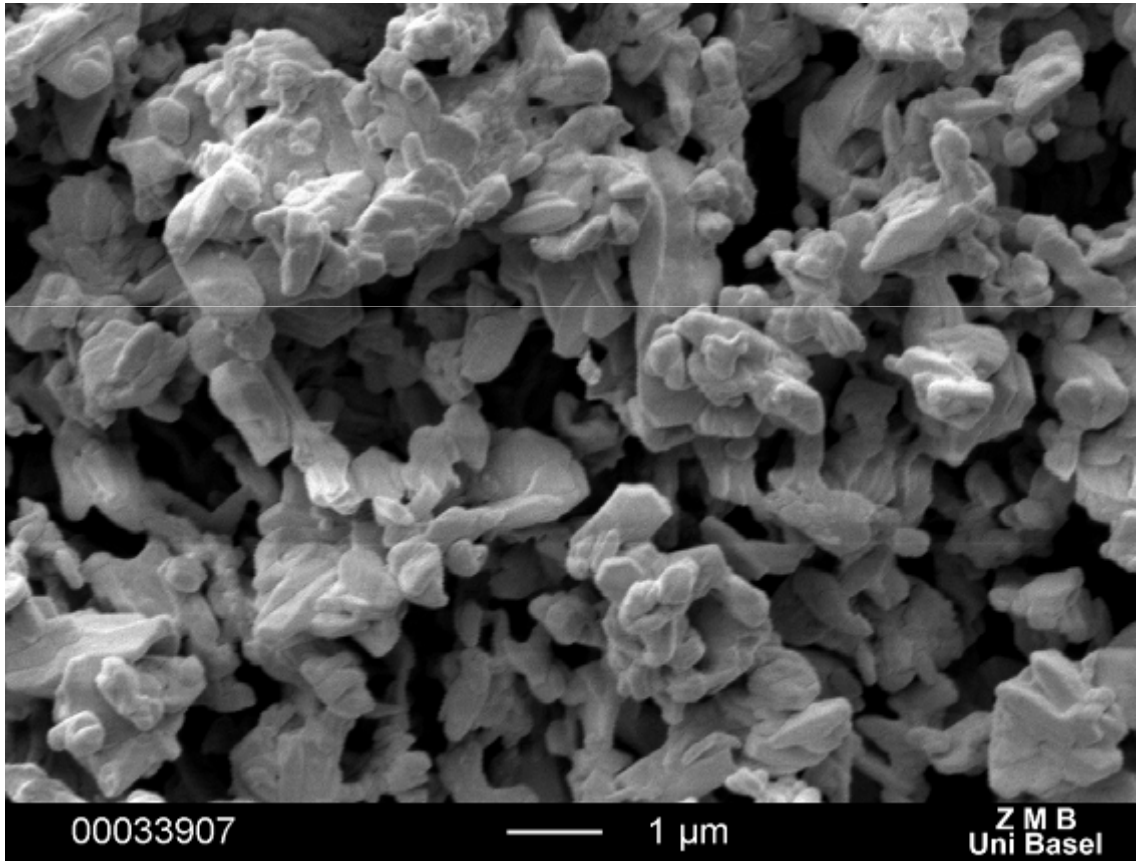
Drying Kinetics: Residual moisture content = f(t) (min!)



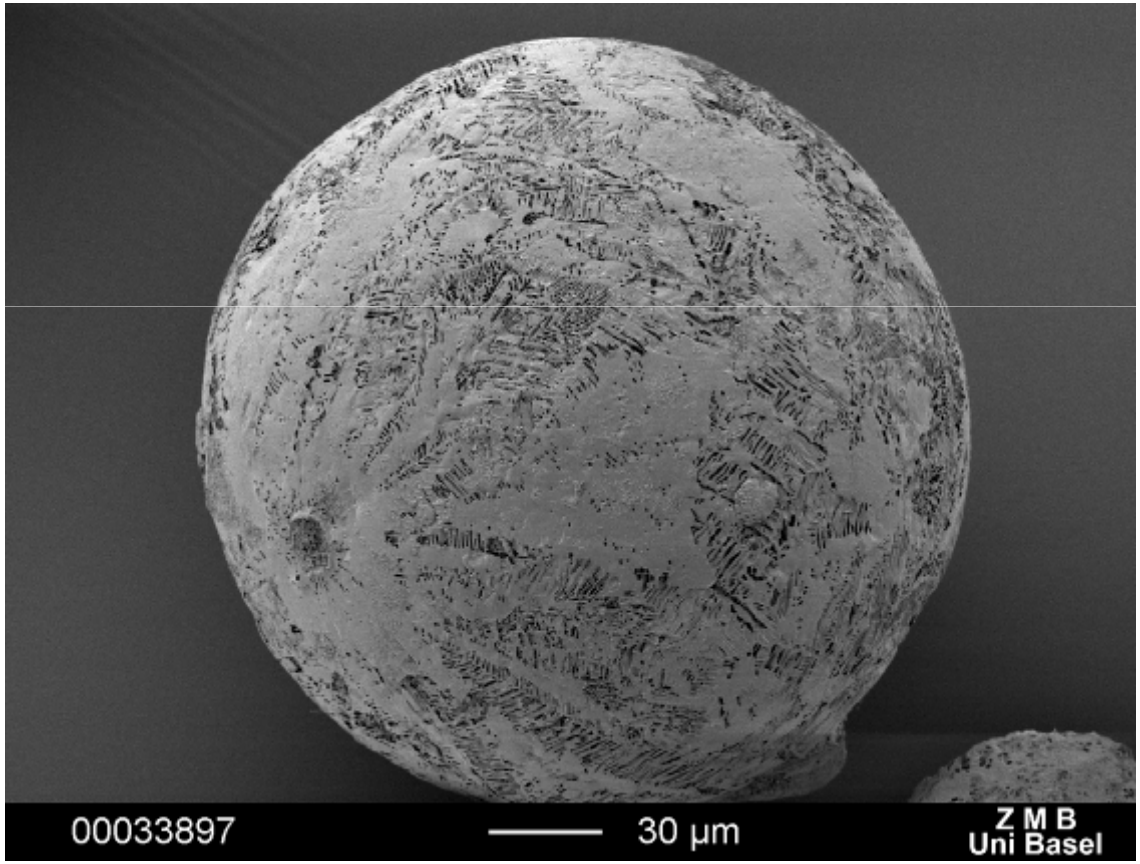
Mannitol (1) 15% solid fraction



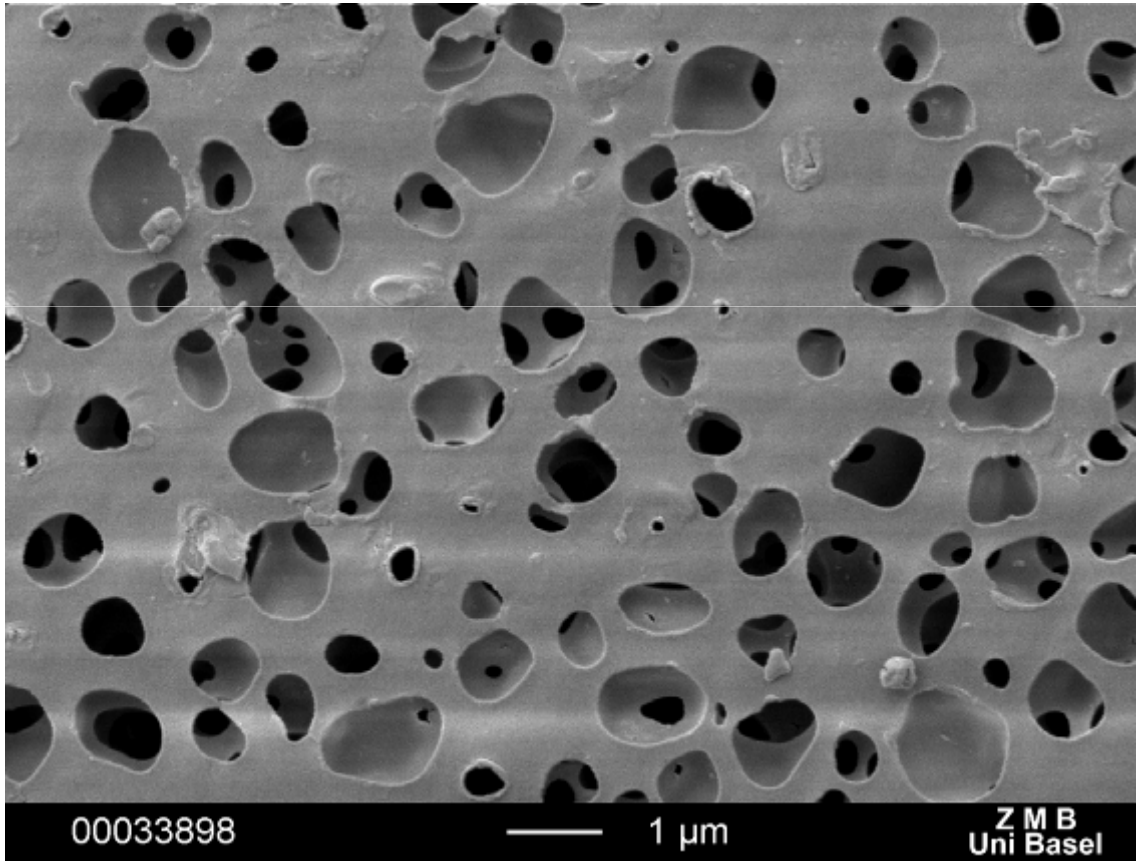
Mannitol (2) 15% solid fraction



Dextran (1) 15% solid fraction



Dextran (2) 15% solid fraction



Vacuum freeze drying	Atmospheric spray freeze drying
Cake	Powder
No further processing	Further processing possible
Long drying cycle >48h	Drying cycle: 2-3 hours
Freezing step critical	Consistent structure of frozen particles
Lab scale process validation is required	Process control by temperature, dewpoint,...
Inhomogeneous drying conditions	Homogeneous due to fluidization
Product in primary package	Product filling required

Conclusions

Atmospheric Spray Freeze Drying is the Process of Choice:

- to **avoid** the critical freezing step of the classical lyophilisation process
- to **prepare** nanocomposites for low water soluble drugs
- and for **temperature and structure sensitive** drugs such as interferones etc.

Conclusions

Spray Freeze Drying compared to classical lyophilisation:

1. Spray Freeze Drying is very robust due to the very fast freezing process of small droplets.
2. The spray freeze drying at atmospheric pressure is a fast process.

– Will Spray Freeze Drying become a Disruptive Technology, i.e replacing classical freeze drying ?

Thank you for your attention

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