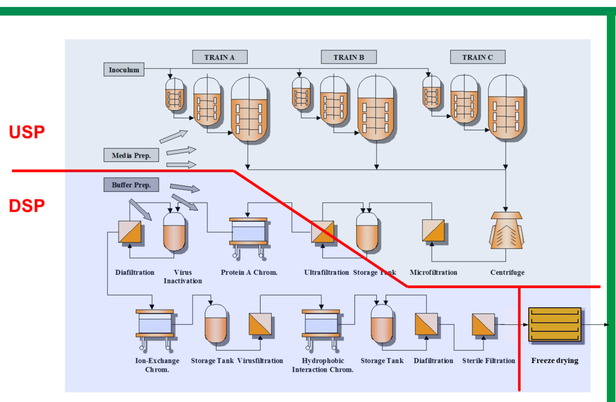
TU Clausthal
Institute for Separation and Process Technology
Prof. Dr.-Ing. Jochen Strube

Digital Twin of Lyophilization for Process Intensification in the Production of Bio-Molecules

A. Juckers[1], P. Knerr[2], F. Harms[2], J. Strube[1]
[1]Institute for Separation and Process Technology, TU Clausthal D-38678 Clausthal-Zellerfeld, Germany
[2]Martin Christ Gefriertrocknungsanlagen GmbH, D-37520 Osterode am Harz, Germany

Introduction

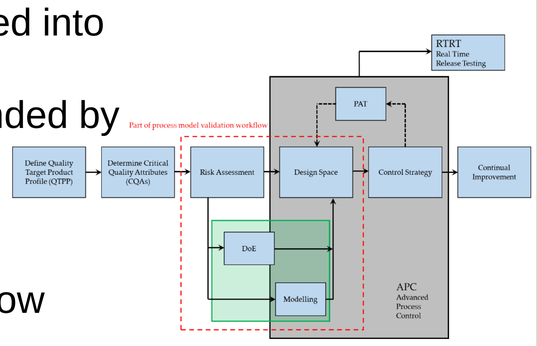
- Lyophilization is used for conservation and preservation of bio-molecules
- Gentle drying conditions are suitable for sensitive products
- 60% of biologics were not available without lyophilization

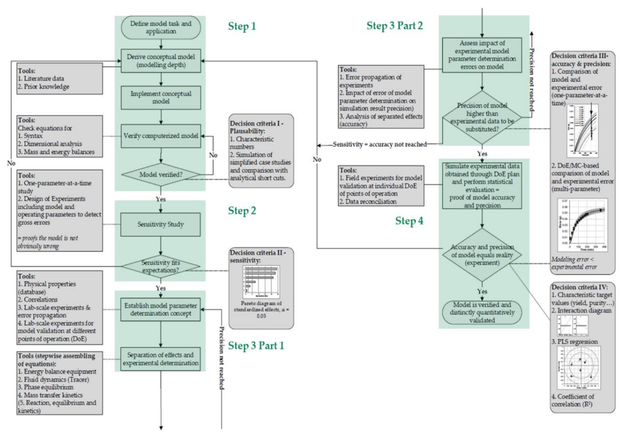


- Process simulation aids process design, optimization and control
- Validation of a physico-chemical process model by a validation concept with an experimental DoE in pilot scale

Model validation workflow

- Model validation can be implemented into Quality-by-Design approach
- QbD is a consistent concept demanded by authorities for data-driven process improvement
- PAT and Modeling are supporting technologies that in combination allow Real time release testing





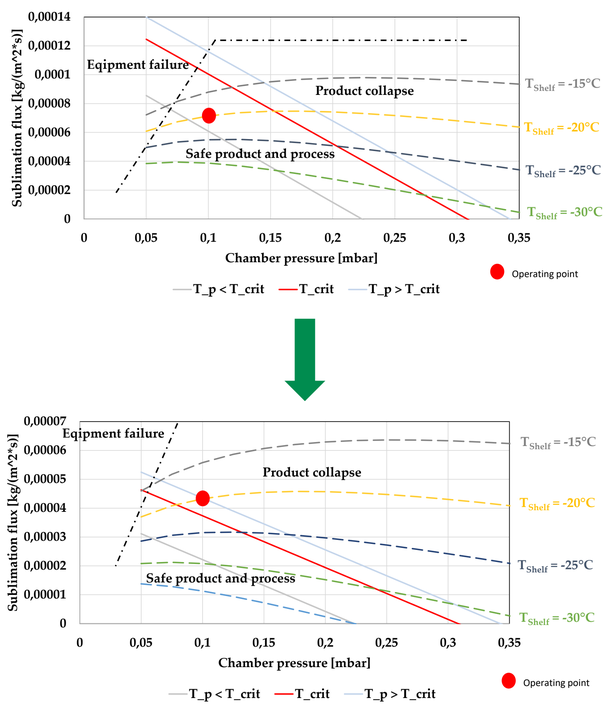
- Reproducible validation process has been used for model development to ensure sufficient accuracy and precision

Model development

- Process models have to take the coupled mass and heat transfer based on the law of conservation into account

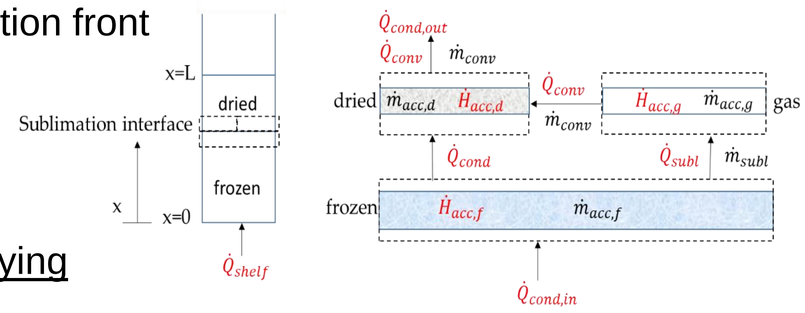
Design space modeling

- Modeling of coupled heat and mass balance under pseudo steady state conditions
- Heat supplied to the vial is completely used for sublimation
- Equipment and product constraint are considered
- Safe process in beginning can change to product collapse during operation
- Model allows technology transfer and Scale-up



Non-steady state modeling

- One-dimensional sorption sublimation model with uniform sublimation front



Primary drying

- Heat transfer modeled by conduction
- Latent heat of sublimation is considered by apparent heat capacity
- Mass transfer by sublimation modeled by pressure difference between sublimation front and chamber pressure

Secondary drying

- Heat transfer modeled by conduction
- Mass transfer by desorption modeled with an Arrhenius approach

Experimental DoE in pilot scale

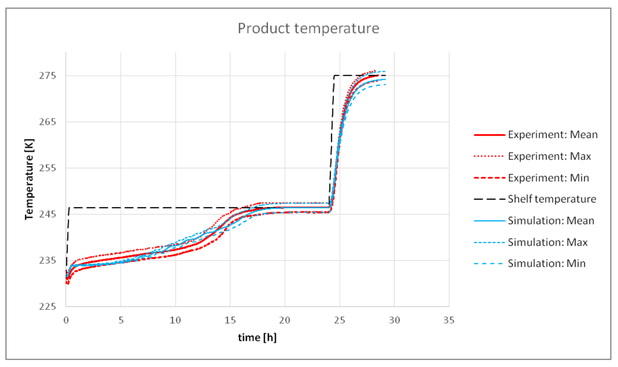
- Plackett-Burman design

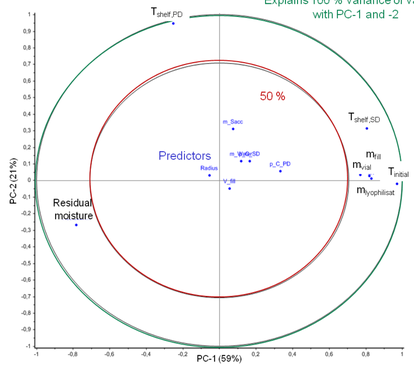
Process parameters	Design range	Unit	Expected influence	Rationale
Shelf temperature (prim. drying)	−35–−25	°C	High	typical temperatures for drying of protein solutions
Chamber pressure (prim. drying)	0.076–0.2	mbar	High	35–90% of ice pressure at lowest temperature
Shelf temperature (sec. drying)	−10–10	°C	High	reasonable range, above collapse temperature
Chamber pressure (sec. drying)	0.01–0.05	mbar	No	reasonable range starting at lowest possible pressure (equipment boundary)
Duration (sec. drying)	2–6	h	Medium	little impact because driving force is defined by pressure and temperature but desorption process has a slow kinetic
Temperature ramp (all phases)			Low	in this study primary drying is always completed, therefore no collapse should occur

Pilot scale freeze dryer Epsilon 2-6D by MartinChrist GmbH applied

Conclusion

- Simulation results show higher accuracy than experimental runs





- Significant parameters are identified with Correlation loading plots
- The process model shows appropriate accuracy and prediction and is therefore successfully validated

References

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