Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Model-based process design for the manufacturing of COVID-19 vaccines

Topic:	**Implementation of mechanistic models for the stability of biopharmaceuticals during and after freezing**
Type:	Master Thesis, or with reduced scope Bachelor Thesis/Semester Project
Starting date:	Summer or Fall 2022
Breakdown:	100% modeling
Advisor:	Prof. Dr. Marco Mazzotti, ML G27, mazzotti@ipe.mavt.ethz.ch
Supervisors:	Leif-Thore Deck, ML G16, deckl@ipe.mavt.ethz.ch

Freezing is an essential process in the pharmaceutical industry to improve the stability and thus shelf life of biopharmaceuticals, such as protein-based formulations or vaccine suspensions. In fact, most of the commercially available COVID-19 vaccines are stored in the frozen state. As the lack of stability is a major burden for most biopharmaceuticals, there is a need for a better understanding and control of the freezing process. [1] While freezing generally increases the shelf life, quantifying the extent of this effect remains challenging, since it depends strongly on both the physicochemical properties of the specific drug and on the freezing conditions. On a high level, one may consider three distinct effects that may affect drug stability in the context of freezing: Cold denaturation, surface-induced denaturation, and freeze-concentration. [2] It is the objective of this work to integrate models for these three phenomena into an existing open source python package for the simulation of the freezing process that was recently developed in our lab. [3-4]

Scope of the Project

The scope of this work is twofold. In a first step, the student will become familiar with the existing freezing model in the lab, and with literature approaches to model the stability of biopharmaceuticals. These literature models are evaluated in detail and some of them eventually are to be integrated into the existing model. By doing so, the student contributes towards the development of a python package that is used in the pharmaceutical industry for the design and optimization of freezing processes.

Secondly, we will conduct case studies with sample formulations to identify optimal freezing conditions at production scale. We will develop freezing strategies that aim at mitigating potential degradation mechanisms, and provide guidelines for freezing professionals in industry and academia on how to design such processes.

Proposed Outline of the Main Project

- Short literature review on the research topic and existing works in this field
- Implementation of existing drying models from literature
- Development of a novel model that provides a physical and mathematical description of the process, and its implementation
- Sensitivity analysis of the model predictions

- Comparison of the model outcomes among the models and validation with experimental data

Requirements

- Solid background in engineering subjects (e.g. Transport Phenomena, Numerics)
- Creative, highly motivated and independent attitude
- Programming skills required (Matlab ok, python better). Coding will be a major part of the project, and you will be able to contribute to an open source python package [4]

Deliverables

Short, schematic reports of what has been done during the week, including methods, results, and discussion and what is planned for the following week should be submitted by email to the supervisors every Friday. The results obtained will be presented in two oral presentations, one about halfway through the project and one at the end.

References

[1] J Wang, Y Peng, H Xu, Z Cui and RO Williams: The COVID-19 Vaccine Race: Challenges and Opportunities in Vaccine Formulation. *AAPS PharmSciTech 21 (2020) 225.* https://doi.org/10.1208/s12249-020-01744-7

[2] A Arsiccio and R Pisano: The ice-water interface and protein stability: A review (2020), *J. Pharm. Sci. 109,7, pp. 2116-2130,* https://doi.org/10.1016/j.xphs.2020.03.022

[3] LT Deck, DR Ochsenbein and M Mazzotti: Stochastic Shelf-Scale Modeling Framework for the Freezing Stage in Freeze-Drying Processes, *Int. J. Pharm.* (2021) in press: https://doi.org/10.1016/j.ijpharm.2021.121276

[4] LT Deck, DR Ochsenbein and M Mazzotti: SNOW – Stochastic Nucleation of Water, (2021), GitHub Repository, https://github.com/SPLIfA/snow/