

INSIGHTS INTO FREEZE-THAW PROCESSES FOR THERAPEUTIC PROTEIN FORMULATIONS

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For transport logistical reasons and for the decoupling of DS and DP shelf-life, most Biologics Bulk Drug Substances (BDS) are frozen and thawed before further processing. There are contradictory reports and publications on the influence of freezing processes - sometimes ultra-fast freezing is worse in terms of increased aggregate formation, sometimes slow freezing is inferior. Effects may only be visible upon subsequent long time storage (1, 2). The influence of the thawing process is usually neglected in the considerations and investigations, although here also protein can be damaged.

Case studies reported in the presentation on various therapeutic proteins show that slow and apparently mild thawing at low temperatures can lead to gelation or precipitation due to protein-protein interactions. Following CFD simulations, we have changed the design of the existing blast freezers and also added fast blast thawing (fig.1). The presentation will introduce experiences with this new blast-freezer-thawer as well as with representative freeze-thaw downscale models applied to formulations of therapeutic proteins. It could be nicely demonstrated that cryo-concentration of a monoclonal antibody and of the buffer agent had the same pattern in the downscale model and in the 2 L at scale bottle (fig. 2). Techniques such as micro CT for studying ice structures and the distribution of formulation components in ice are also presented.

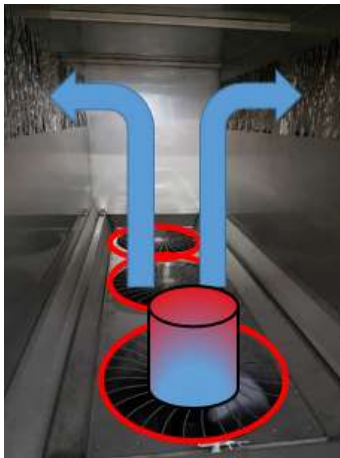


Figure 1: Novel Blast Freezer Thawer

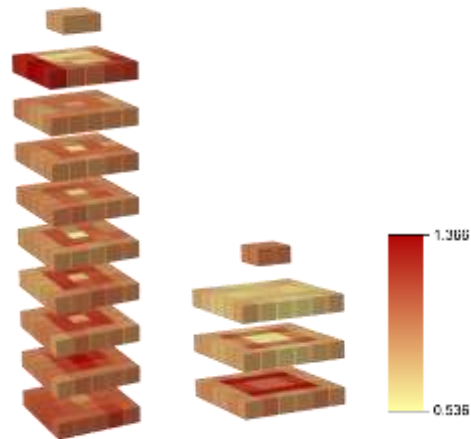


Figure 2: Cryo-concentration factor of mAb in a 2 L bottle (left) and in the downscale model (right)

References:

- (1) B. Connolly et al., J. Pharm. Sci. 104:4170 – 4184, 2015
- (2) Satish K. Singh et al, Pharm. Res. 28:873 – 885, 2011
- (3) Oliver Blümel et al., Comparison of cryoconcentration in PET bottles and an innovative scale-down device, Poster at Conference “Freeze Drying of Pharmaceuticals & Biologics”, September 19 – 21, 2018, in Garmisch, Germany