IMPLICATIONS OF POROUS-FLOW IN THE DESIGN OF FREEZE-THAW SYSTEMS FOR BIOPHARMACEUTICALS AND RATIONAL SCALE-DOWN METHODOLOGY.

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Porous-flow through an ice matrix is a ubiquitous phenomenon during both freezing and thawing of biopharmaceutical formulations. During the freezing process, when the ice dendrites are formed, the proteins and excipients are excluded from the ice front. A concentrated aqueous solution is entrapped by the ice dendrites, creating what is called a mushy layer. By the action of gravity or pressure forces, the concentrated solution may flow through the ice matrix, disrupting the homogeneity of the mixture at the macro-scale. The concentrated solution is transported away from the mushy layer, creating spots of more concentrated solution in some regions of the container. During the thawing process, the same phenomenon occurs and is responsible for the strong stratification of the biomixture observed in the final liquid solution. Macro-concentration in the ice matrix and final stratification of the liquid solution are adverse phenomena that may trigger protein aggregation. Therefore, well-designed scale-down methods should mimic these adverse conditions that happen at large scales.

In this presentation, the impact of porous-flow on the macro-cryoconcentration and solution stratification after thawing will be analyzed inside bags, for vertical and horizontal heat transfer directions, using both freeze-thawing experiments and CFD simulations. In particular, the impact of the temperature and solution composition on porous-flow magnitude during thawing is examined based on the observed stratification during bottom-up unidirectional thawing (Fig. 1). Based on these experimental and theoretical insights, new rational designs for freeze-thawing scale-down systems are proposed for bags. This methodology is illustrated for the particular case of bottom-up freeze and thawing of bags, using a scale-down system that works with a sample of 27 mL to mimic a system of 10 L.

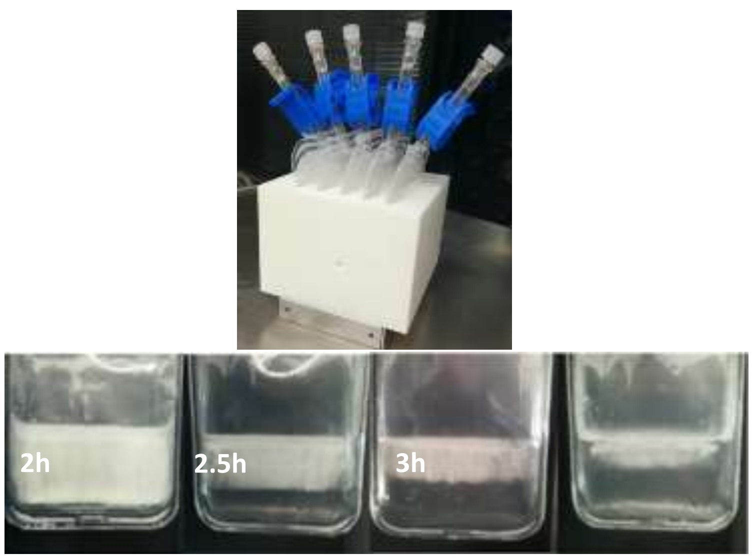

Figure 1 – Top) Bottom-up unidirectional scale-down device for bags. Bottom)Time-lapse of 27 mL bags initially at -30ºC thawed unidirectionally at 26 ºC (100mg/mL Sucrose solution, 5 mg/mL BSA, 3gpL NaCl.),