Predicting the phase behavior during freeze-drying of biopharmaceuticals

A tool to optimize excipient selection in formulation and process development

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Freeze-drying (lyophilization) remains one of the dominant strategies for long-term stabilization of biopharmaceuticals. The biopharmaceutical is thereby embedded in an amorphous phase of several excipients (e.g. cryoprotectants such as sugars), preserving its native state and activity during storage. Aside protein stability, choice of the excipients also defines process parameters of the lyophilization process, e.g. drying time. Choice of excipients and determination of these process parameters is usually performed through costly and time-consuming experiments. Within this work, we developed a hybrid (predictive) approach to facilitate the excipient choice and give easy access to the aforementioned process parameters.

Freeze-drying (lyophilization) is frequently used as the formulation method of choice when it comes to sensitive biopharmaceutics. The lyophilization process can be divided into two major process steps. The first step is freezing. During this step, the solid (ice) phase is formed, leading to a concentrated amorphous (excipient) phase surrounding the ice particles. The excipients, the biopharmaceutical, and a bit of water are then present in the amorphous phase. The second step is the actual drying, where the majority of water is sublimated by reducing the pressure below the sublimation pressure of ice at the given freezing temperature. Most important parameters that need to be known are: (1) the lowest possible temperature at which freezing should be performed, (2) the amount of residual water that is present after freezing. The latter intrinsically defines the drying time.

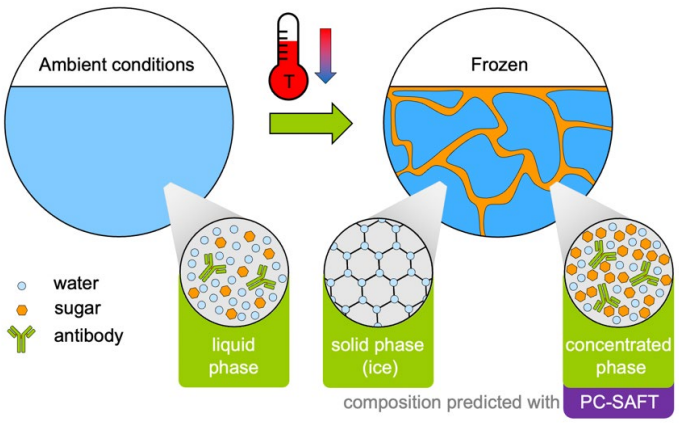

Figure 1: Schematic representation of the freezing step during freeze drying. Initial state at ambient conditions is shown on the left. Sugar and antibody are dissolved in water. The state after freezing is shown on the right. An ice phase and a concentrated amorphous phase have formed. The excipients initially dissolved in the liquid phase can now be found in the amorphous phase.

For a given excipient (mixture), the exact amount of excipients in the amorphous phase (vice versa the residual amount of water in the amorphous phase) is defined by the intercept of the glass-transition temperature (of the amorphous phase) and the solubility of water (being a function of temperature and type of excipient(s)). This process step is nicely visualized in Figure 1 and the two separate phases are illustrated in blue and orange.

Applying our hybrid approach, we determined the glass-transition temperature of the amorphous phase using one single experiment. This then allowed us to calculate the composition of the amorphous phase after freezing using the thermodynamic model PC-SAFT. We experimentally validated the approach for common single excipients used in freeze-drying e.g. sucrose and trehalose, for excipient mixtures of sucrose with the osmolyte ectoine and for excipient/protein mixtures of sucrose/BSA. It was shown that the approach precisely predicts the composition of the amorphous phase after freezing and thus dramatically reduces the effort required in state-of-the-art approaches. It can therefore be used for fast screening of potential formulation compositions during formulation and process development.

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