freezing. In formulations including sodium chloride as a tonicity modifier, the salt crystallizes around its eutectic melting temperature of −21 °C. Other excipients such as mannitol, glycine, disodium phosphate, or sorbitol also have a tendency to crystallize in a frozen state, which could generate undesirable stability issues. These crystallizations generally do not occur at early stages of frozen storage, and such stability issues may not be apparent during short-term stability studies. For this reason, unexpected problems such as aggregation and/or precipitation are often not observed until after 6–9 months of frozen storage. Due to these considerations, the decision to use a frozen formulation needs to be made after thorough research and investigation.

Lyophilized Formulation

Many biopharmaceutical companies choose a lyophilized formulation as the initial formulation if proper expertise and resources are available to support rapid development. The primary reason for considering an early development lyophilized formulation is the higher probability of success in achieving a stable formulation. If the company has established a strong intellectual property for the product and no competition is anticipated in the market, the lyophilized formulation could potentially be continued for commercial purposes.

A lyophilized formulation is also recommended if the product has limited stability in a liquid state. As most degradation reactions are facilitated by surrounding water molecules, e.g., hydrolytic reactions, deamidation, and proteolytic activities, the removal of water can be an effective approach to enhancing stability.

As briefly discussed in Sect. 5.1.1, proteins may experience undesirable structural changes during dehydration. Therefore, proper formulation development is required to stabilize proteins in order to achieve suitable lyophilized formulations. In addition to stability, a lyophilized formulation should satisfy other attributes such as an elegant appearance, consistent moisture content, rapid reconstitution, etc., so comprehensive knowledge around specific excipients' compatibility to lyophilization is essential for proper formulation development.

Formulations developed for lyophilization may be stored as a frozen liquid in cases where lyophilization resources or equipment are not readily available. The development of an ideal lyophilization cycle as well as the manufacturing of lyophilized drug product would require several months worth of additional research, additional drug substance, and a properly validated facility. This part of development can be delegated as the commercial formulation development stage.

Liquid Formulation with Limited Expiry

For proteins with demonstrated stability in a liquid state at refrigerated storage with limited expiry can be introduced as an initial formulation. This will require