dilution of the product. Some of this dilution can be minimized by using a N_2 gas purge but still may be limited by how much of the product can easily flow out of the system at the higher viscosity at final targeted DP concentration. A strategy that has been used successfully to concentrate mAbs and increase yield is to use high temperature to lower viscosity during the TFF unit operation. The pressure drop for the TFF system can be decreased at higher temperatures (Figure 7.1(a)) as the viscosity of the solution decreases (Figure 7.1(b)), resulting in increased flux ($L/m^2/h$) at a given pressure drop (Figure 7.1(c)). Such a strategy has been used successfully for a mAb where the process temperature was increased from 23 to 46 °C, resulting in a twofold decrease in viscosity and a twofold increase in the filtration flux (Winter, 2008; Liu, Ma, Winter, & Bayer, 2010). As much as 600 g of mAb has been processed to 150 mg/mL with a 96.2% yield using such a modified TFF unit operation. Implementation of this strategy does require extensive study of the stability of the mAb at the elevated temperature. Thus, the choice of a formulation that minimizes degradation at elevated temperature goes hand in hand with the TFF process design. Also investigation of impact of higher temperature on bioburden may require addition of microorganisms at different temperatures to ensure there is sufficient control of growth during the elevated temperature process.

Development of alternative processes/formulations for manufacturing of high-concentration dosage forms

Although TFF is the most commonly used unit operation to manufacture a high-concentration protein/mAb final DP, any drying technique that can be scaled up for manufacturing can be used. An example of this is the use of freeze-drying to produce a solid dosage form, which can be reconstituted using a lower volume than that loaded into the vials before freeze-drying (Figure 7.2). One of the drawbacks for such a process is that not only is the mAb concentrated upon reconstitution but also are all the excipients. This raises a level of concern regarding the final tonicity of the reconstituted product since preparations that greatly exceed isotonicity may result in impacting adsorption of the drug at the injection site as well as result in increased pain and tissue damage (Chapter 6). Lowering the concentration of excipients may circumvent this problem, but there needs to be a sufficient amount of stabilizer to ensure minimization of degradation during the freeze-drying process. As an example, the tonicity of a freeze-dried formulation for subcutaneous (SC) delivery of an IgG1 mAb at high concentration was dependent on the loading concentration of the mAb. The final concentration after reconstitution is given below:

$$C_F = C_L V_L / (V_R + V_S) \tag{7.1}$$

where C_F is the final concentration after reconstitution, C_L is the loading concentration of mAb, V_L is the loading volume V_R is the volume of diluent added for reconstitution, and V_S is the volume contributed from the remaining solids. The expected final concentration