NPH, Premixed 70/30 or 50/50) in a fill–finish facility which typically runs manufacture process in campaign mode with appropriate change over controls.

Aprotinin

Aprotinin is a polypeptide that inhibits the action of trypsin, chymotrypsin, and plasmin and is used as a hemostatic in several surgical procedures [34, 35]. Peters et al. describe the successful bulk crystallization of aprotinin variant by employing a statistical design of experiments (DOE)-based approach and a conventional screening approach which was followed by DOE. Figure 4 describes the two crystal forms of aprotinin variant. Monoclinic (plate-shaped) crystals (Fig. 4a) are formed with sodium chloride, whereas clusters of tiny plate-like crystals (Fig. 4b) grew with ethanol and magnesium sulphate.

Both the described crystallization conditions were successfully applied at scale in manufacturing process. The crystals obtained were bulk lyophilized after successive water washings. Furthermore, the crystals could easily be reconstituted in buffer at pH 7.8. Both of these crystallization steps could be employed either as a hold step in the process or the final storage of purified bulk drug. Such an approach is very similar to that taken for insulin, reiterating the possibility of employing freeze-drying/lyophilization as a final storage or hold step for crystallized bulk biopharmaceuticals.

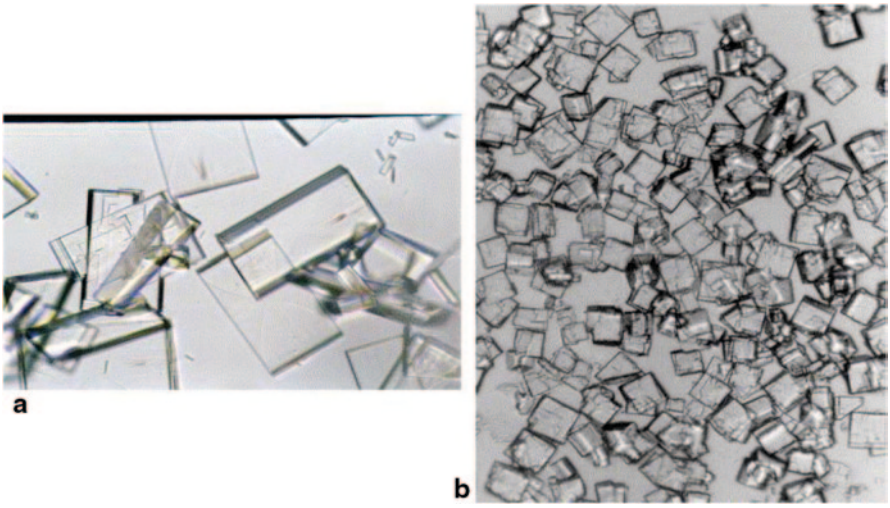

Fig. 4 Photograph of crystals of the aprotinin variant. **a** Conditions: 5 mg/mL protein, pH 4.9, 50 mM NaCl, *T*: 20 °C, 300 µL microbatch. Approximate size of the average crystal: 10–20 µm length, 7–14 µm width. **b** Conditions: 2.5 mg/mL protein, pH 5.0, 13 % ethanol, and 5 mM magnesium sulfate, *T*: 20 °C, 300 µL microbatch. Approximate size of the average crystal: 3–5 µm length, 2–5 µm width (Adapted with permission from [36])