



**Fig. 13** OCT-FDM 2D images of 5% BSA/sucrose (25%/75%) product formulation showing the onset of shrinkage at  $-22.3^{\circ}\text{C}$  [11]. *OCT-FDM* optical coherence tomography freeze-drying microscopy

vials, filled with 25%/75% (5% total solids) BSA/sucrose formulation. The low-temperature drying cycle based on the LT-FDM collapse temperature determination ( $-28^{\circ}\text{C}$ ) was operated at a shelf temperature of  $-22^{\circ}\text{C}$  and 65 mTorr chamber pressure to achieve an average product temperature of  $-34^{\circ}\text{C}$  during primary drying, measured using TCs placed in the bottom center of sample vials. The secondary drying shelf temperature was  $40^{\circ}\text{C}$ . The primary drying time for this batch was 20 h. The high-temperature drying cycle based on the OCT-FDM shrinkage temperature ( $-22.3^{\circ}\text{C}$ , no internal collapse) was operated at a shelf temperature of  $50^{\circ}\text{C}$  and 300 mTorr chamber pressure to achieve an average product temperature of  $-23^{\circ}\text{C}$ . The secondary drying shelf temperature was  $50^{\circ}\text{C}$ . The primary drying time for this aggressive cycle was 4 h, an 80% reduction in time compared to the low-temperature process. The authors reported that macroscopic product collapse was not observed in vials from either cycle, although product shrinkage from the vial wall was observed in vials from both batches, consistent with reports and prior experience drying sucrose-based formulations. Additional product quality assessments were performed on the dried product from each batch to enable comparison of  $T_g$  (high temp:  $65.6^{\circ}\text{C}$ , low temp:  $72.2^{\circ}\text{C}$ ), residual moisture (high temp: 1.7%, low temp: 1.2%), and specific surface area, SSA (high temp:  $0.138\text{ m}^2/\text{g}$ , low temp ( $0.760\text{ m}^2/\text{g}$ ). *Scanning electron microscope* (SEM) analysis was also performed on dry product samples from each batch showing a reduction in the number of pores and an increase in the pore size for the product dried at the higher primary drying temperature based on the OCT-FDM-based collapse temperature determination, consistent with the SSA measurement. Thus, the authors not only observed differences in the dry product characteristics but also demonstrated agreement between the batch freeze-drying data and the OCT-FDM observations. No collapse