primary drying. A characteristic powder X-ray diffraction pattern was found for this product and archived in technical reports for future reference.

After analyzing the temperature trends of this product through primary drying, it was decided to use as a consistent metric the initial temperature plateau early in primary drying as that to which we correlated the failure modes. Microcalorimetry as well as laboratory- and pilot-scale freeze-drying studies were used to determine that, for a properly frozen and annealed product, at −10°C this product suffered from microcollapse due to mannitol crystal melting, at −6°C some vials (particularly those at the edge of a shelf or tray ring) collapsed at the edge of the cake, and temperatures at or above −3°C yielded product with slow reconstitution. Photographs were taken of acceptable product as well as those that should be classified with various types of defects. The images were included in manufacturing procedures for product inspection to ensure continuity over the ensuing years.

Primary Drying Optimization

The failure modes testing of the product defined the maximum temperature during primary drying (specifically the initial plateau early in primary drying) to be −10°C. This is a relatively high value, which is due to the presence of a significant quantity of crystallized mannitol. The next step was to minimize the duration of primary drying with new set points for shelf fluid inlet temperature and chamber pressure. A range of these parameters was tested, and product quality attributes as well as overall duration of primary drying and maximum sublimation rate were measured. It was found that with the cycle currently in place, the product dried at a maximum rate of 0.45 kg/hr·(m^2 of product loading). The drying rate is per square meter of product loading—this is with a hexagonal packing. It was found that the primary drying duration could be reduced from an average of 60 hours to just 34 hours if the primary drying shelf fluid inlet temperature was changed from −5°C to +20°C, and the chamber pressure was increased from 110 to 200 mTorr. The new primary drying conditions (with product frozen and annealed properly) were found to yield excellent product quality, however, the product dried at a higher maximum rate of 1.0 kg/hr·(m^2 of product loading). The next section shows results of freeze-dryer capability measurements to determine if the dryers could reliably handle this higher sublimation rate.

Freeze-Dryer Capabilities Assessment

Figure 4 shows the results of the combined primary drying optimization and the freeze-dryer capability assessments. The *y*-axis of both panels is the maximum sublimation rate during primary drying, normalized by square meter of shelf space loaded with this product. The green squares and diamonds show the drying rate generated by product for the old and new processes respectively. Panel A shows the results for dryers C through J fully loaded with product. Panel B shows the results for the current partial load (108 trays) as well as full load (144 trays) in freeze-dryers A and B.

From Figure 4A, the interpolated line for dryers C and D shows that they would be able to accommodate a rate of about 1 kg/hr (m^2 of product loading) at the current pressure of 110 mTorr, but none of the others would. In particular, dryer J had always shown stress in the form of increasing condenser coil