completed the drug product is present as a bulk solid matrix devoid of frozen water (ice) with the remaining unfrozen water dispersed in the solid matrix. The lyophilizer chamber pressure is maintained at a low level during secondary drying, often not changing from the primary drying chamber pressure. The shelf temperature is usually increased to deliver additional energy to the system to drive the desorption of water from the product matrix. Secondary drying is a relatively high-temperature process, often ranging from +25°C to +40°C. The maximum secondary drying temperature is dependent on the glass transition temperature (T_g) of the dry product. This temperature is typically determined by DSC of the dry cake. Note that the dry cake glass transition temperature is inversely dependent on the moisture level in the lyophilized powder. The secondary drying temperature selected should allow a significant margin for the critical temperature in case powder of slightly higher moisture is encountered during secondary drying. As a general rule, the ramp to secondary drying should be relatively rapid since the risk should be minimal and goal is typically to reduce total cycle time. However, in those cases for products which have a relatively low critical temperature (or one which is very sensitive to moisture content), a slower ramp may be preferable to allow desorption to occur during the ramp time and provide for a slightly lower moisture content when the final secondary drying temperature is reached. Secondary drying time allows for some flexibility in lyophilization cycle design. Although removal of moisture is still critical, total desorption of all unfrozen water is not a requirement of the end of secondary drying as total sublimation is for all frozen water (i.e., ice) is to the end of primary drying. Though many dual chamber packages can be stoppered within the lyophilizer similar to vial products, there are still a number of dual chamber products on the market that are stoppered externally after being unloaded from the lyophilizer. This means that the cake will have a residence time between lyophilizer unloading and final stoppering where the cake is exposed to its environment. This exposure should be under controlled humidity conditions, and the exposure time should be minimized to prevent additional moisture uptake.

Loading Configuration

A unique consideration for dual chamber packaging is the configuration of the syringes in the dryer. Syringes cannot be loaded into a lyophilizer by conventional tray or trayless systems since some variety of cartridge holder is required. Loading systems for syringes can vary significantly; however, there are four broad categories of loading systems. When developing a lyophilization cycle for product in a dual chamber package it is critical to understand the potential impact of the loading configuration on the drying cycle (e.g., cartridge holder design, contact surface area for heat transfer, and cartridge spacing). A loading system that is representative or identical to the commercial process is essential for proper cycle development. This is true of traditional (vial) cycle development and of even greater importance for dual chamber packaging. The basic categories of syringe holders are discussed below.

Packed Cassette

A diagram of cartridges loaded in a packed cassette configuration is shown in Figure 12. The packed cassette or "shoe box" configuration consists of cartridges tightly packed against one another in a "box" or cassette (usually stainless steel).