

In a dedicated designed stirred drying chamber the material to be dried is frozen. Due to stirring motion the material, being a liquid, paste or solid, will be transformed into solid granules. The granules can have sizes and shapes which are controlled by the mixing characteristics of the machine.

Once the freezing step is completed the drying chamber is closed and vacuum is applied. After evacuation of the freezing agent the sublimation process will start. From this stage the product temperature is dictated by the vacuum level. During sublimation the heat is supplied through the jacket and efficiently distributed throughout the product by the stirrer. The initially coarse granules will gradually reduce in size due to the sublimation of the connecting ice structure in between the frozen material. The released dried particles will make up a loose powder.

Towards the end of the drying process when most of the frozen solvent is sublimated the product temperature will start to rise. Finally the product temperature will equalize the wall temperature, indicating that the drying process is finished. By then all material is transformed into a fine and loose powder, after breaking the vacuum the dryer can be discharged easily from the dryer vessel, assisted by the transporting characteristics of the mixing element.

Figure 2 shows images of freeze-dried material from the Hosokawa Active Freeze Dryer and a standard tray freeze-dryer, providing evidence that the Active Freeze Dryer can achieve similar particle sizes of dry product. Per the manufacturer, the minimum pressure that can be currently achieved is approximately 400 mTorr, and they have not yet developed a sterile version.

Meridion Technologies GmbH promotes a bulk freeze-dryer, *LyoMotion*, that tumbles its contents in a rotating cylinder that is mounted horizontally, as shown in Fig. 3 (Meridion Technologies n.d.). Heat transfer is by thermal radiation and heated product-contact surfaces. They also offer spray-freezing technology (*Spray-Con*) that can be connected to their *LyoMotion* dryer.

IMA Life North America has applied for patents for using spray-freezing to create frozen droplets, followed by freeze-drying in an agitated tank, as shown in Fig. 4 [8]. The spray-freezing concept includes separate product and liquid nitrogen spray nozzles at the top of the freezing tank.

A concern with all of these concepts is that one must be mindful of product loss by deposition on the internal surfaces of the equipment; however, this disadvantage is also a concern for spray-drying.

Aseptic Crystallization and Drying

Aseptic crystallization/precipitation and drying is a current technology that is commonly used for nonsterile as well as sterile APIs. The process stream entering the crystallization step of the API manufacturing is sterile filtered, using 0.2 μm filters, into pre-cleaned and sterilized tanks, and the product, after crystallization, is filtered and dried in aseptic fluid drying step. This last stage of the API manufacturing process is carried out under International Organization for Standardization (ISO) 5, aseptic conditions. This part of the process will need to be validated for asepticity by media runs simulating the process.