of reconstitution. So, primary drying must be performed maintaining the sublimation interface temperature below the formulation specific upper limit: the collapse temperature.

During the drying process, a mass and heat transfer balance can be established; the heat to sublimate is supplied by the combined effects of conduction, convection, and radiation from the heated shelves. The sublimation process, being endothermic, produces a cooling effect over the product. The balance of both heat input and removal dictates the equilibrium temperature of the sublimation interface.

There can be two types of sublimation processes, one where the limiting factor lays in the heat supply or the opposite where the bottleneck is the transport of the sublimated vapors, directly affecting the heat removal.

The strategies to run a cycle in each case are very different and antagonist. It is not infrequent having cycles with heat transfer, as the limiting factor, at the beginning of the primary drying, experiencing mass transfer limitation at the end.

It is in this way that one can understand why, in some cases, there are processes that may experience collapse at the end of primary drying: as the sublimation proceeds, the thickness of the already dry layer increases and, if the crystals are small, their conductance for the generated vapors is decreasing, reducing the sublimation mass flow and thus its associated cooling effect. So, if the heat input remains constant, the sublimation interface temperature rises significantly. If the process is performed at a product temperature close to its maximum temperature, this can lead to the collapse.

To define the lyophilization process, a "recipe" is specified, which is a set of shelf temperatures and chamber pressures versus time steps, but this does not guarantee repeatable conditions for freezing and also does not guarantee that the variable of interest, that is, the sublimation interface temperature is perfectly defined.

It is not uncommon listening in lyophilization courses that "in this process there are two independent variables, shelf temperature and chamber pressure, and when they are fixed, then the dependent variable, product temperature, becomes also fixed." The problem is that the product temperature is not only a function of these two mentioned variables, but at least two others: the heat transfer resistance (how difficult is the heat supply from the shelf to the sublimation interface) and the vapor flow resistance in the dry structure (how difficult it is for the sublimated vapors to flow through the dry layer) that increases as the drying proceeds.

Heat transfer resistance depends on the actual barriers between the sublimation interface and the fluid circulating within the shelves. And as there are three different mechanisms of heat transfer, each one will involve different parameters. Conduction will depend directly on solid layers, materials, and contact between these layers (shelf metal thickness, the eventual use of trays, vial bottom shape and thickness, and product height, etc.). Convection will strongly be influenced by the dimensions of the interstitial space between the product container (usually glass) and the tray or the shelf, and the chamber residual gas density (directly related to pressure). Radiation can induce batch heterogeneity depending on the exposure of each vial to its direct sight of the surrounding surfaces, so the edge vials will be influenced by the chamber walls in a different way than the central ones (Fig. 1).