



Fig. 1 State diagram of a binary solution of sucrose and water (See text for detailed explanation. Adapted from [1])

concentrated solution T_g' , which corresponds to $\sim 80\%$ sucrose content ($W_{g'}$). Note that there is $\sim 15\text{--}20\%$ water (depicted at point $W_{g'}$) in the sucrose freeze concentrate at T_g' . Below T_g' , the solute exists as glass separated from ice crystals. Although the value of T_c is constant, T_g' varies with the measurement technique. A frequent term used while designing a lyophilized formulation is the collapse temperature (T_c) of a formulation. T_c is the temperature above which a frozen concentrated matrix loses its physical structure due to viscous flow as detected using freeze-drying microscopy. In order to produce a stable lyophilized formulation, the temperature of the product (depicted by “F” in Fig. 1) during primary drying should be below T_g' , T_c , and most importantly T_c . Therefore, estimation of T_g' , T_c , and T_c is the first step in designing a lyophilization process. Since primary drying is the longest phase of a lyophilization cycle, optimization of process conditions during this step results in shorter processing times.

The primary and secondary drying processes differ by definition, with the former being related to ice sublimation and the latter to water desorption. These processes influence or facilitate phase transitions. This is primarily due to the presence of high energy states of the compounds or molecules at the very beginning (freezing) of the process, which transform to the lower energy states by the end of the lyophilization process. It is equally important to state that the presence of high- or low-energy solid forms and their interconversion is dependent on the lyophilization process design and also on the complex interaction of coexisting compounds/excipients in the formulation. In an un-optimized formulation, phase transitions from a high-energy to a low-energy form have been shown to occur following lyophilization during storage with adverse impact on the formulation stability [2, 3].