

## **Effect of Process Variables on Physical State of Mannitol in Tert-Butyl Alcohol - Water Systems**

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Mannitol, a highly crystalline excipient, is traditionally used as a bulking agent in freeze-dried formulations. The crystallization behavior of mannitol in frozen aqueous solutions has been extensively investigated. Our goal is to investigate the influence of tert-butyl alcohol (TBA) as a cosolvent on the extent of mannitol crystallization, both during prelyophilization solution cooling and heating of the frozen solutions. We intend to explore the potential advantage of retaining mannitol partially amorphous in frozen solutions. Solutions of mannitol (5% w/v) in TBA-water systems of different compositions (10 - 40% w/v TBA) were prepared. Changes in the physical form of mannitol and TBA, in frozen aqueous systems, were studied by low temperature X-ray diffractometry (XRD, D8 Advance, Bruker instruments) and by differential scanning calorimetry (DSC). The solutions were cooled from RT to -50 °C in a DSC (Model 2920, TA Instruments), held for 10 min and then heated to 25 °C at heating rates of 1 and 5 °C/min. Selected compositions were also subjected to low temperature XRD studies. Solutions were cooled from RT to -50 °C at 1 °C/min. Frozen solutions were gradually heated to 25 °C and XRD patterns were collected at selected temperatures.

The DSC heating curves of unannealed frozen ternary solutions revealed a sequence of thermal events which could be attributed to two glass transitions, crystallization exotherm, melting of metastable eutectic (TBA - ice), its recrystallization, melting of the stable eutectic and melting of either TBA hydrate or ice. XRD helped identification of phase transformations of crystalline solute phases during warming of frozen solutions. The XRD peaks characteristic of TBA dihydrate and heptahydrate were observed when frozen solutions were warmed from -50 °C to 10 °C (10 – 40% w/v of TBA). The intensity of TBA dihydrate peaks decreased whereas that of TBA heptahydrate increased. In addition to different crystal forms of TBA, XRD analysis of frozen 20% w/v TBA solution showed the presence of  $\delta$ -mannitol, while, the frozen 30% w/v TBA did not show the presence of crystalline mannitol. Crystallization of mannitol in TBA-water frozen system is a complex interplay of the formulation composition and processing parameters. Selection of TBA-water mixture of appropriate composition provides a potential strategy to modulate mannitol crystallization during freezing or freeze-drying.