CRYSTAL STRUCTURE OF D-MANNITOL HEMIHYDRATE

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D-mannitol is widely used as an excipient in pharmaceutical products. In addition to its employment in oral formulations, it finds extensive use in products prepared by freeze-drying. Recently, the formation of a mannitol *hydrate* during the freeze-drying of aqueous mannitol solutions, has been reported (Cavatur and Suryanarayanan, Pharm. Dev. Tech. **3** (1998) 579; Yu et al, J. Pharm. Sci. **88** (1999) 196). Mannitol hydrate is quite unstable and readily transforms to anhydrous mannitol polymorphs, and thus its presence in a freeze-dried formulation can have serious implications on product stability. For the same reason, a detailed characterization of mannitol hydrate was not possible, and the hydrate stoichiometry remained unknown.

The objective of this investigation was to carefully control the freeze-drying conditions so as to first isolate and then characterize the mannitol hydrate. Since freeze-drying was the only viable method to obtain mannitol hydrate, structure solution using a single crystal was not a feasible option. Therefore, synchrotron X-ray powder diffraction and simulated annealing methods were used to solve the crystal structure.

To prepare mannitol hydrate, aqueous mannitol solutions (5% w/v, filtered through 0.2 μm membrane filter) were cooled from 25°C to -50°C at 1°C/min in a tray freeze-dryer and held for 3 hours. The chamber pressure was then set to 100 mTorr and the sample was heated to -30°C at 1°C/min. During this heating cycle, the sample was held at -45, -40, -35 and -30°C for 40, 40, 20 and 20 hours respectively. The temperature was then decreased to -35°C, and held for 20 hours to complete the drying. XRD, DSC and TGA results indicated that mannitol exists as a hemihydrate ($C_6 H_{14} O_6 \cdot 0.5H_2O$). Synchrotron data were collected on the X3B1 beamline at the National Synchrotron Light Source, on a mannitol hydrate sample sealed in a 1.5 mm diameter glass capillary, at -23ºC. Monochromatic X rays of wavelength 1.1507 Å were used.

The diffraction pattern indicated a partial dehydration of the mannitol hemihydrate, based on the presence of peaks attributed to anhydrous δ- and β-D-mannitol polymorphs. Consequently, a Le Bail fit to the mannitol hemihydrate phase was performed simultaneously with a Rietveld refinement of the additional phases. The simulated annealing program PSSP was used to solve the structure, which was subsequently refined by Rietveld analysis using the program package GSAS. It was determined that mannitol hemihydrate crystallizes in P1 space group, with a = 9.8963 Å, b =10.5424 Å, c = 4.7860 Å, α = 102.589°, β = 86.092°, and γ = 116.079°. The unit cell contains two dissimilar D-mannitol molecules and one water molecule, forming a hydrogen bonding pattern significantly different from that seen in the anhydrous polymorphs.