ABSTRACT: The effects of excipient crystallinity and water content on the physical stability of salmon calcitonin (sCT) in a spray-dried powder for inhalation have been investigated. sCT was dissolved in water with and without mannitol and then spray dried using a Büchi 190 spray dryer. The spray dried powders were stored for 5 days at 0, 29, 51, 58, 69, and 84% relative humidity at ambient temperature. The crystalline content, water content, secondary structure, and aggregation rates were determined for each powder immediately following spray drying and after storage at various relative humidities. In addition, the water sorption isotherms and reactivity to water vapor were determined using DVS and isothermal calorimetry, respectively. No sCT aggregation occurred during the spray drying process. Crystallinity depended on the amount of mannitol in the formulation. Powders containing up to 50% mannitol were fully amorphous, and those containing 70 and 90% mannitol contained some crystalline polyol. The powders remained aggregate free for over 2 years when stored below the critical RH (e.g., <20% for the powder containing 30% mannitol). Above this RH, sCT aggregation increased as a function of time. The amount of aggregate observed correlates with the amount of intermolecular β-sheet formed, determined by FTIR. The sCT aggregation rate in powders containing 70% mannitol was significantly lower than that in powders containing 30% mannitol at all RH tested, presumably because of a higher ratio of amorphous mannitol to sCT, which inhibits the formation of β-sheet structure. Moisture-induced crystallization of mannitol was observed in all powders stored at RH >50%. The moisture induced thermal activity trace (MITAT) offers a useful description on the physical stability of the spray dried powders. In conclusion, spray drying sCT and sCT/mannitol mixtures yields dry powders that contain physically intact peptide. In addition, sCT aggregation and mannitol crystallization in spray dried powders can be prevented during long-term storage if stored in low humidity environments, which can be easily assessed by MITAT.
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