PROCESS EFFECTS ON THE PROPERTIES OF SPRAY-FREEZE-DRIED POWDERS

C. Sonner[1], Y.-F. Maa[2] and G. Lee[1]

[1] Department of Pharmaceutical Technology, Friedrich-Alexander University, Cauer Str.4, 91058 Erlangen, Germany
[2] Powderject Technologies Inc, 6511 Dumbarton Circle, Freemont , CA 94555

Introduction

As former investigations have shown, spray-freeze-drying can be used as a method for the preparation of dry powders suitable for various applications [1].
To study the mechanism of particle formation during this process, solutions of two well-known excipients, trehalose and mannitol, were spray-freeze-dried and the resulting powders were characterized. Both substances may be suitable for later use in formulations containing pharmaceutical proteins. Initially, the main points of interest were the process conditions influence of solution's solid content and of the storage time before starting the freeze-drying cycle of the samples.

Experimental Methods

Materials

D(-)-Mannitol was purchased from Merck (Darmstadt, Germany), Trehalose dihydrate was obtained from Sigma (Munich, Germany). Distilled Water was used for all experimental work.

Spray-Freeze-Drying

For each of the two excipients, aqueous solutions of different solid content were prepared. An ultrasonic nozzle (Sonotek, 120 kHz) was used for atomization. Each solution was sprayed into a round metal bowl of diameter 15cm filled with liquid nitrogen continually agitated by a magnetic stirrer bar. The spray droplets froze immediately on contact with the liquid nitrogen. The liquid feed rate was 3.5 ml/min. On completion of spraying, the bowl was immediately transferred to a lyophilizer (Christ, Germany) which had been pre-chilled to -50°C. Up to six samples could be prepared in one experiment. The freeze dryer was subsequently held for a further 30min at -50°C. A vacuum of 0.1 mbar was then applied to the chamber and the shelf temperature increased to minus 20°C to induce primary drying. Primary drying time was 30h. To induce secondary drying, the shelf temperature was raised to 20°C and held for 15h.

Powder Characterization

The morphology of the spray-freeze-dried powders was examined using scanning electron microscopy (SEM) on a Amray 1810 T microscope. The powders were gold sputtered on an Al sample holder.
Residual moisture of the powders was determined by Karl Fischer Titration (Schott, Germany). Samples were dissolved in water-free methanol/formamide (2:1) prior to titration.
Wide-angle X-ray diffraction was performed at 25°C on a Phillips Model TW 1730.
For examination of the thermal transitions of the powders a differential scanning calorimeter (Polymer Laboratories) was used. Samples were sealed in Al pans and repeatedly heated and cooled between 25°C and 90°C at 10°C/min.
Porosimetry measurements were performed on a Porosimeter 2000 and a Macropores unit 120 (Carlo Erba Instruments).

Results and Discussion

Powder Morphology

Spray-freeze-dried particles all showed a spherical shape, sometimes being slightly aggregated.
For mannitol a sponge-like, porous structure was visible [Fig.1], XRD showed a fully crystalline substance. The average particle diameter appears to be approx. 40 µm
Trehalose particles had a smooth surface with an obvious internal porous structure [Fig.2] and were completely amorphous according to XRD. The average particle diameter is also approx. 40µm.The density of these very light powders was measured by mercury porosimetry.

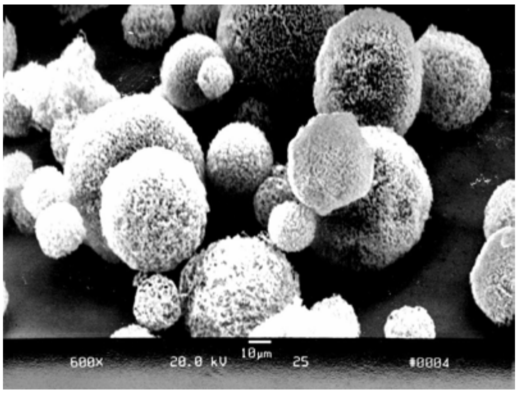

Fig.1: SEM of spray-freeze-dried Mannitol

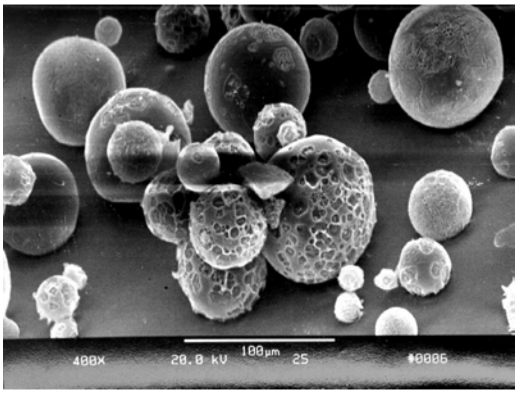

Fig.2: SEM of spray- freeze-dried Trehalose

Influence of solid concentration

For pure mannitol, solutions of 20 and 30% solid content were prepared and sprayed under the same conditions. The powder from the more concentrated solution showed the δ-modification of mannitol [2] when examined by XRD. At the lower concentration, a mixture of the α-, β-, and δ-modifications resulted [Fig.3]. The crystallisation behaviour is influenced by the concentration of the mannitol solution.

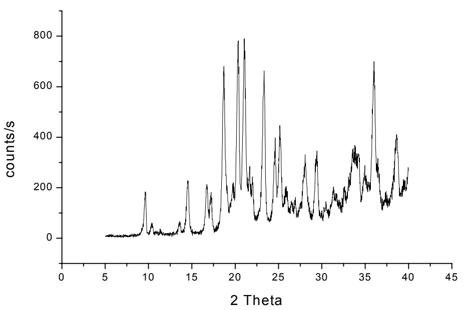

Fig.3: XRD of mannitol powder prepared from a 20% solution

Influence of storage time before freeze-drying

Six batches of a 20% w/w trehalose solution were sprayed and each one was immediately transferred to the pre-chilled drying chamber. After starting the drying cycle, the first sample had therefore been stored at -50°C for three times longer than the last one. This difference was not detectable in the particle morphology, but show differences in water content and T_g of the products:

Table 1:Properties of spray-freeze-dried trehalose

storage time [min]	water content [%w/w]	T_g[°C]
100	6,05	49,06
74	6,12	48,88
67	6,95	43,42
49	7,23	39,26
37	7,44	39,65

For mannitol powders prepared in the same way, no differences in water content were detected. The latter was always approx. 1.15%. The XRD indicated, however, different modifications. During storage at –50°C in the freeze-dryer, ice crystals in the sample can grow. Large crystals will preferably sublimate in the primary drying, resulting in dryer products.

Conclusions

Spray-freeze-drying produced free flowing, light particles of these two excipients. The powder properties are, however, highly dependent on the process parameters. Further investigation parameters is necessary for process validation.

References

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[2] Kim A.I., Akers M.J., Nail S.L. The Physical State of Mannitol after Freeze-Drying: Effects of Mannitol Concentration, Freezing Rate, and a Noncrystallizing Cosolute J. Pharm.Sci. **87** 931-935 (1998)