

Lyophilisation of mannitol and NaCl solutions in serum vials

Lyovapor™ L-200 Pro

1. Introduction

In this Application Note sodium chloride (NaCl) and mannitol are used for freeze drying experiments. The unambiguous crystal structure of NaCl renders this salt a model compound. In contrast, mannitol is well known to crystallize in different polymorphs¹ and it may form hydrates².

Nevertheless, mannitol is the most used bulking agent for freeze dried pharmaceutical formulations.

2. Experimental

3 mL of 5 % aqueous mannitol or NaCl solutions (50 g/L) were transferred into the vials with a volumetric pipette (70 vials of each solution). Then, the samples were frozen overnight in a deep freezer at -40°C on a stainless steel tray.

After 24 hours of deep freezing the vials were transferred on the steel tray to the Lyovapor™ L-200 for freeze drying. The collapse temperature was set to 30 °C. For unknown formulations, it is recommended to determine the collapse temperature by means of a freeze drying microscope. Furthermore, a safety temperature margin can be programmed to protect the sample from collapsing.

The shelf temperature itself was chosen such that it does not exceed 20 °C at the end of the primary drying and 25 °C at the end of the secondary drying. For more information about the drying sequence, please see reference 3.

After drying, the residual moisture content of nine mannitol and NaCl samples, positioned on the shelf diameter, were analyzed using a halogen moisture balance heated to 110 °C. Therefore, the samples were ground in a mortar and transferred to the moisture analyzer within 30 seconds.

3. Results and Discussion

The vials containing pure mannitol that were located on the shelf diameter are shown in Figure 1. Generally, all vials contained a homogenous freeze dried mannitol or NaCl cake.



Figure 1: Freeze dried mannitol samples analyzed for its residual moisture.

To determine the drying efficiency of the Lyovapor™ L-200, the residual moisture content of nine mannitol samples positioned on the tray diameter were analyzed using a halogen moisture analyzer. The results of the measured residue moisture contents are shown in Table 1.

Mannitol samples, independent of their position on the shelf, contained less than 2.0 % moisture after the freeze drying process.

Table 1: Results of the residual moisture content analysis after freeze drying mannitol solutions with the Lyovapor™ L-200.

Vial	Initial weight of freeze dried sample [g]	Weight at end of analysis [g]	Residual moisture content [%]	Drying efficiency [%]
1	0.107	0.105	1.87	98.13
2	0.100	0.098	2.00	98.00
3	0.113	0.112	0.88	99.12
4	0.122	0.121	0.82	99.18
5	0.111	0.110	0.90	99.10
6	0.116	0.115	0.86	99.14
7	0.121	0.120	0.83	99.17
8	0.108	0.107	0.93	99.07
9	0.116	0.114	1.72	98.28

We found that the mannitol samples positioned in the middle of the shelf contained marginally less residual moisture than the samples placed on the outer radius of the shelf. For NaCl this pattern was not observed. The residual moisture contents for NaCl varied randomly between 0.79-1.59 %. This finding may indicate that during the freezing process the fraction of mannitol hydrate formed is greater on the outer than on the inner shelf area.

Furthermore, it is likely, that some water is adsorbed on the sample while preparing it for the residual moisture analysis. Hence, the drying efficiency is probably higher than reported.

Strategies to remove more moisture are i) increasing the drying time, ii) increasing the temperature during secondary drying and iii) annealing².

4. Conclusion

With the Lyovapor™ L-200, a high drying efficiency of was achieved for the water removal of a mannitol model formulation and a NaCl solution. For both compounds, the optical appearance of the dried cake was uniform, and no collapsed cakes were observed.

5. References

- Kim, A.I.; Akers, M.J.; Nail, S.L. J. Pharm. Sci. **1998**, 87 (8), 931-935.
- Yu, L.; Milton, N.; Groleau, E.G.; Mishra, D.S.; Vansickle, R.E. J. Pharm. Sci. **1998**, 88 (2), 196-198.
- BUCHI Application Note, 256/2017 Lyophilisation of an aqueous mannitol formulation.