COLLAPSE TEMPERATURE MEASUREMENT BY FREEZE-DRY MICROSCOPY AND TRANSFERABILITY TO FREEZE DRYING PROCESSES: INFLUENCE OF SOLUTE CONCENTRATION ON COLLAPSE BEHAVIOR AND EFFECT ON CYCLE DESIGN

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RESULTS & DISCUSSION

For all three excipient solutions $T_c$ as measured by FDM showed a great dependence on total solid content of the solution (Fig. 1-3). At a low total solid content measured $T_c$ was low with an increase at higher concentrations. The overall difference between the minimum and the maximum of determined $T_c$ is 5 K for sucrose. 3 K for trehalose and 8 K for PVP 10 kDa. At very high concentrations hygroscopic effects of the dried matrix lead to a decrease in $T_c$ for the total sugar (Fig. 3). Calculated $T_c$ for sucrose revealed the $T_c$ at a total solid content of 0.11 g/g and for trehalose as -27.0°C at 0.2 g/g. These alterations are not reflected in measurements of dynamic surface tension (Fig. 4). Values for all concentrations were detected in the same magnitude with a linear dependence of surface tension on total solid content. Viscosity data show differences for sucrose and trehalose with slightly higher values for sucrose. This may explain the unequal collapse behavior. For PVP 10 kDa the molecules overlap for solutions with a high total solid content [1] so that the exponential increase is much stronger compared to that of the sugars.

Transferability of $T_c$ (FDM) on Freeze Drying Processes:

As illustrated in Pic. 5-6, the "onset" of collapse was determined in this study when the first fissures or holes in the structure appeared as bright spots in the image. This measurement methodology is found consistent for very low (e.g. 2%) and high (e.g. 20%) total solids. $T_c$ with a 25% sucrose solution determined to be -33.6°C by FDM. For all low concentrated sucrose solutions, microcapsule in the structure was found after the freeze drying cycle, even when freeze dried under very conservative conditions ($T_c$ setting: -36°C, $T_p$(max): -37.9°C, Tab. 1) [2]. In contrast, no shrinkage was found for a 10% Trehalose solution and more severe process conditions. Here, the $T_c$ was measured more than 3 K higher by FDM compared to the lower concentrated solution. Due to the capillary structure, the 10% cake structure is much more rigid (Pic. 7-9) although freeze dried at much higher product interface temperature (32°C). For a 25% sucrose concentration the system tolerated both a $T_r$(max) (MTM): -35.8°C ($T_c$ setting: -32°C and -34°C ($T_c$ setting: -26°C) within a full structural loss (Pic. 12). However, it is important to note that SEM images of sucrose and the $T_c$ setting of -28°C showed much more droplet formation in the structure (indicating viscous flow) compared to a $T_c$ of -30.2°C. The utilized VILASTIC Viscoelasticity Analyzer is a capillary viscometer with oscillatory flow principle. It was connected to a chiller unit (temperature between 0.00°C and 1.00°C). The utilized VILASTIC Viscoelasticity Analyzer is a capillary viscosimeter (VILASTIC Viscoelasticity Analyzer is a capillary viscosimeter with oscillatory flow principle. It was connected to a chiller unit (temperature between 0.00°C and 1.00°C).

CONCLUSIONS

For the determination of $T_c$ on total solid content (observed for trehalose, sucrose and PVP 10 kDa solutions) it is reflected in viscosity values of the solutions at 0°C, but further investigation is necessary to explain unequal collapse behavior. A case study for different concentrated sucrose solutions during vial freeze drying clearly indicates that higher concentrated solutions may tolerate higher product temperatures which is consistent with collapse data obtained by FDM.

REFERENCES