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The effect of molecular weight of polyvinylpyrrolidone on the crystallization of co-lyophilized sucrose

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Protein drugs can be stabilised in the dry state by including lyo/cryo protectants such as sugars within the final formulation. The glassy structure of such sugars is thought to protect the conformational structure of proteins. However, a sugar glass, being thermodynamically unstable, will transform to a crystalline form under normal conditions, thereby excluding the protein molecule and rendering it biologically inactive. It is therefore of great importance to maintain the glassy state of such sugars. Polyvinylpyrrolidone (PVP) has been found to inhibit the crystallisation of amorphous sucrose (Shamblin et al., 1996). Since PVP of different molecular weight (MW) was shown to exhibit different glass transition temperatures (Maria del Pilar et al., 1992), such polymers may possess different effects on the crystallisation of amorphous sugars. Therefore, it was the aim of the present work to investigate the effect of MW of PVP on the crystallisation of co-lyophilised sucrose.

Sucrose was co-lyophilised with 2.5% and 5% w/w PVP with MW 10,000, 24,000, 40,000 and 300,000. Freeze-drying was carried out for 48 h at a shelf temperature of - 40°C and a pressure of about 270 mTorr. The samples were transferred to a vacuum oven and allowed to dry at 24°C for 12 h before drying for a further 12 h at 40°C. Differential scanning calorimetry (DSC) was employed to measure the dynamic crystallisation temperature (T_c) and isothermal crystallisation induction time (t_c) of sucrose. T_c was recorded as the temperature corresponding to the maximum of the exothermic peak associated with the crystallisation of amorphous sucrose during DSC scanning at a heating rate of 10 K min^{-1} between 20° and 220°C, whilst t_c was taken as the time period required for the exothermic peak to occur at a specific temperature (e.g. 85°C).

All sucrose-PVP mixtures were shown to possess higher (ANOVA, $p < 0.01$) T_c of sucrose than the freeze-dried sucrose alone. For example, freeze-dried sucrose exhibited a T_c of around 85°C, which was increased to over 100°C in the presence of PVP. PVP of MW 300,000 consistently resulted in a T_c of sucrose, which was significantly ($p < 0.05$) higher than those brought about by other PVP of smaller MW. Surprisingly, PVP of MW 10,000 produced significantly ($p < 0.05$) higher T_c of sucrose as compared with PVP of MW of 24,000 or 40,000. For example, the mixtures containing 2.5% PVP 10,000, 24,000 and 40,000 exhibited sucrose T_c of 115.5 ± 1.8, 105.1 ± 2.2 and 104.8 ± 3.2 °C, respectively. Increasing the concentration of PVP from 2.5% to 5% also resulted in a significant ($p < 0.05$) increase in the T_c of sucrose.

Freeze-dried sucrose showed a t_c of 1-2 min at 85°C. An almost 10-fold increase in sucrose t_c was observed when it was co-lyophilised with 2.5% PVP of MW 24,000 or 40,000. However, co-lyophilisation of sucrose with 2.5% PVP of MW 300,000 resulted in a t_c of the sugar (89.1~95.6 min), which was approximately 7 times higher than that in the presence 2.5% PVP of MW 24,000 (13.5~15.3 min) or 40,000 (11.7~12.8 min). PVP 10,000 resulted in a higher t_c of sucrose than PVP 24,000 or 40,000 when presented at the same weight concentration. Increasing PVP concentrations from 2.5% to 5% generally resulted in a 6-7 fold increase in the t_c of sucrose. However, the mixtures containing 2.5% PVP of MW 300,000 exhibited a t_c of sucrose, which was close to those of the mixtures containing 5% PVP of smaller MW. These results suggest that PVP of MW 300,000 may be more efficient in inhibiting the amorphous-to-crystalline transformation of the sugar as compared with PVP of smaller MW. Such polymers may have a crucial role in the stabilisation of proteins and peptides by maintaining the glassy structures of sugars.

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