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Thermal analysis of a freeze dried formulation—the effect of drying time

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In recent years the development of protein and peptide pharmaceuticals has increased significantly. Freeze drying may be employed to present such drugs in a stable form, which may be easily reconstituted prior to parenteral administration.

Knowledge of the temperature at which the glass transition of freeze dried products occurs is important because processing or storage above this temperature can cause collapse of the cakes, stickiness and/or crystallisation and associated loss of activity (Sun et al, 1996). An important factor influencing the glass transition of a formulation is the quantity of water present.

In this study, modulated differential scanning calorimetry (MDSC: details of this technique are given elsewhere e.g. Coleman and Craig 1996) has been used to determine the glass transition temperatures of protein formulations that have been freeze dried for different lengths of time.

The formulations contained lactate dehydrogenase (5μg/ml), sucrose (17mg/ml) in sodium phosphate buffer (10mM, pH 7.0 at 25°C). 2ml portions were quench frozen in liquid nitrogen and transferred to the pre-cooled (-65°C) freeze dryer (Edwards Modulyo) shelf where they were left for between 3 and 72 hours.

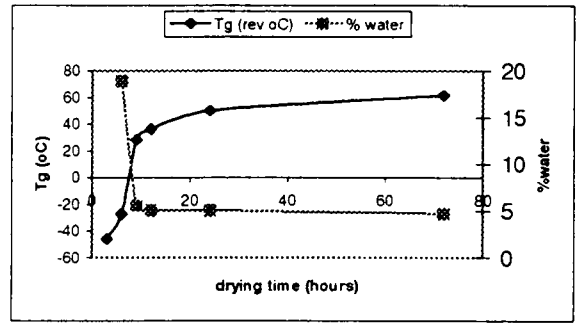
Samples were analysed immediately after production. MDSC analysis (TA Instruments DSC 2920) was carried out in heating mode using 2°Cmin^{-1} heating rate and modulation of 0.3°C over 60s period. Karl-Fischer analysis (Metrohm 701 KF Titrino) was performed to measure the water content of the samples.

The glass transition temperature (Tg) of the formulations increased with increasing drying time (Table 1). This is because the amount of residual water, which acts as a plasticizer, is reduced (see Figure 1). Even small increases in water content give rise to large depressions of Tg (note difference between 24 and 72 hour sample). The crystallisation temperature (Tcrys) also increased in this manner.

Table 1 The effect of drying time on properties of freeze dried samples

Drying time (hours)	Tg (rev) (°C)	Tcrys (total °C)	%water
3	-46.1±1.8	/	/
6	-27.5±2.5	/	18.9±2.8
9	28.1±0.3	80.1±3.0	5.57±0.6
12	36.1±7.3	80.8±5.3	5.05±0.3
24	49.9±3.2	85.7±6.1	5.05±0.1
72	61.6±0.6	102.4±2.2	4.71±0.1

Figure 1 Effect of Drying Time on Water content and Tg



These experiments indicate that MDSC may prove useful as an analytical tool in the development of freeze drying protocols for proteinancious materials as well as a quality control technique that could predict the physical stability of the freeze dried product.

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