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Determining α-relaxations with isothermal microcalorimetry to develop freeze dried products with improved shelf life from a thermodynamical point of view.

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The stabilization of pharmaceutical proteins in a lyophilized product depends on various parameters. At least as important as the formulation itself are the thermodynamic properties of the resulting matrix. The latter should contain amorphous, glassy phases which are most suitable to stabilize the protein. However, amorphous solids are not in a thermodynamic equilibrium and possess an excess in enthalpy compared to their crystalline counterparts or a supercooled liquid. Thus, the matrix will slowly relax during storage to release its energy excess. This process can be measured with isothermal microcalorimetry resulting in relaxation curves as seen in Figure 1.

With this curves τ^{β}, a stretching parameter, can be calculated that describes the curve progression. A flat curve with a low heat power integral results in a high value of τ^{β}.

Several studies showed that protein degradation over time correlates with the value in τ^{β} [1]–[3]. A formulation with a flat relaxation curve, and thus a high τ^{β}-value, correlates with a better long term protein stability from a thermodynamic point of view.

As described in Figure 1 there are different possibilities how to increase τ^{β}. Both of the displayed methods work with a relatively high thermal energy input at the end or during the freeze drying process which can lead to an initial protein damage.

We now try to receive a better understanding of the different matrix treatment methods to improve the process how to increase τ^{β}. It is extraordinarily important to find an optimal balance between undesired initial protein damage while increasing τ^{β} and potentially improved long term stability. Our experiments show promising results concerning kinetic temperature boarders in connection with sample morphology and/or ingredients of the lyophilized product. Furthermore, we suggest a model how to determine remaining energy excess in a matrix after certain tempering temperatures have been applied.

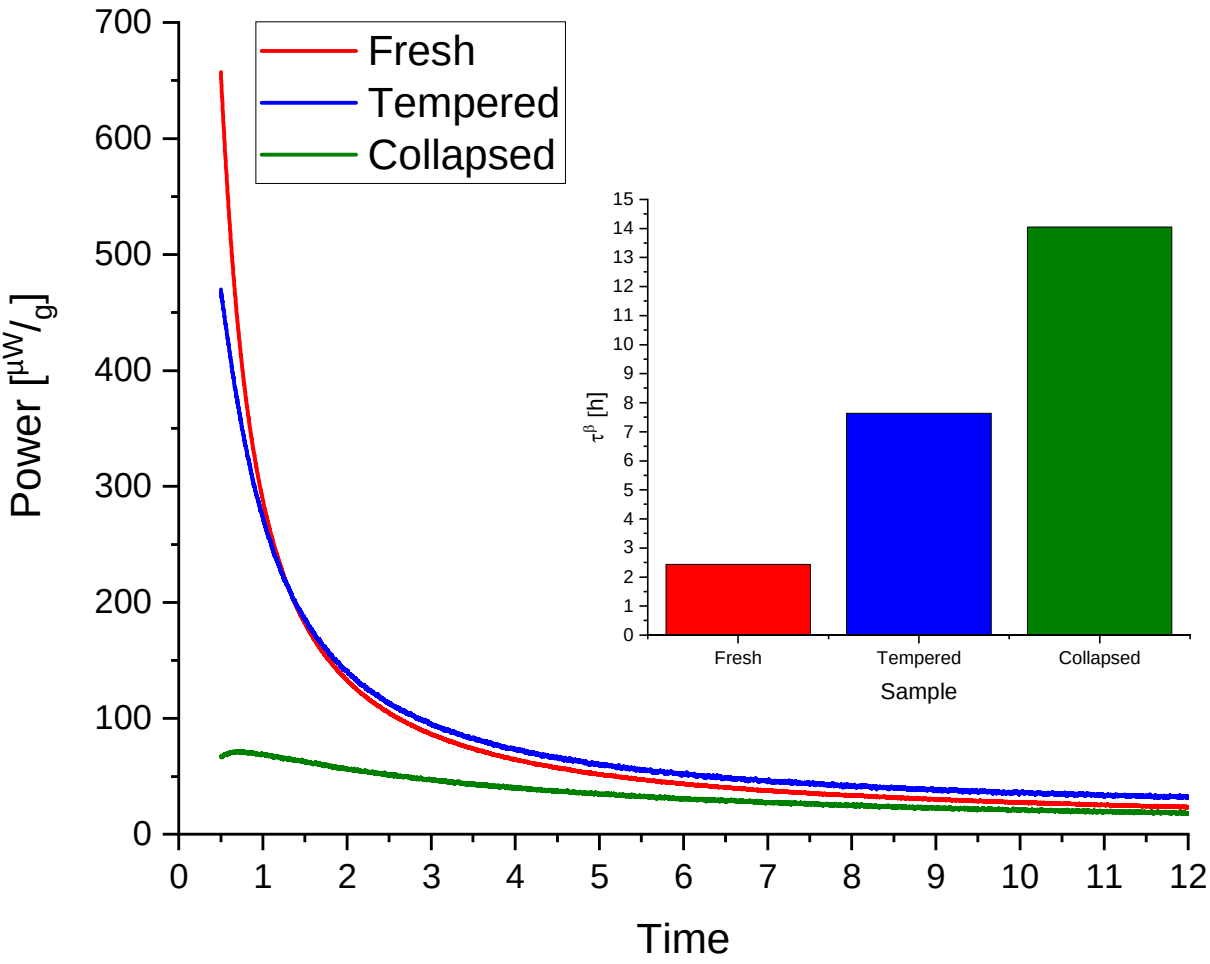

Figure 1: Resulting relaxation curves of the same sugar based freeze dried formulation treated with different processes. Measurement was performed with an isothermal microcalorimeter at 55 °C. Fresh: Measured immediately after the lyophilization process; Tempered: Measured after sample exposure to 25 °C for 7 days; Collapsed: Aggressive lyophilization recipe that led to structural collapse of the sample during the lyophilization process. The sample was measured immediately after the lyophilization process; The small inset shows the corresponding τ^{β}-values.

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