Empirical Correlation for Predicting Equilibrium Moisture Content in Sugar/Protein Mixtures During Freeze-Drying

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Predicting the equilibrium moisture content of a dried cake during freeze-drying is essential for understanding the desorption kinetics of bound water and ensuring the final product's quality and stability. The weighted-average model [1] is frequently used for mixture formulations; however, this correlation often falls short in complex systems, such as sugar/protein mixtures, due to interactions between sugar and water monolayer sites on dried proteins [2,3].

The Sucrose/BSA mixture is used as a model formulation, focusing on the protein fraction range between 0 to 0.7. Experimental data, shown in **Figure 1**, shows the same trend as in literature [2,3]: the moisture content at the end of the freeze-drying cycle is not a static figure, but is subject to dynamic changes influenced by the protein composition of the mixture and the temperature conditions during the freeze-drying process. This observation indicates that moisture content may need to be expressed differently than previously acknowledged by linear correlations.

Using scaled moisture content data converted from Figure 1, an empirical correlation is introduced to more accurately predict the equilibrium moisture content for different protein fractions and temperatures. This method has been validated by extensive freeze-drying experiments conducted on a variety of protein fractions at different secondary drying temperatures, using a laboratory-scale lyophilizer. **Figure 2** presents comparisons between measured equilibrium moisture content and model-predicted values. The input for the model is moisture content data of pure-components (BSA or Sucrose). The results underscore the limitations of using linear models and the necessity for an empirical approach in predicting the equilibrium moisture content of the freeze-dried mixture formulations. The equilibrium moisture content measured at two different temperatures supports the notion that it is not merely a function of temperature but also of the specific interactions within the protein/sugar matrix. This study lays the groundwork for a more refined understanding of moisture dynamics in freeze-drying and opens up avenues for further investigation into the molecular interactions at play in the lyophilization of complex mixtures.

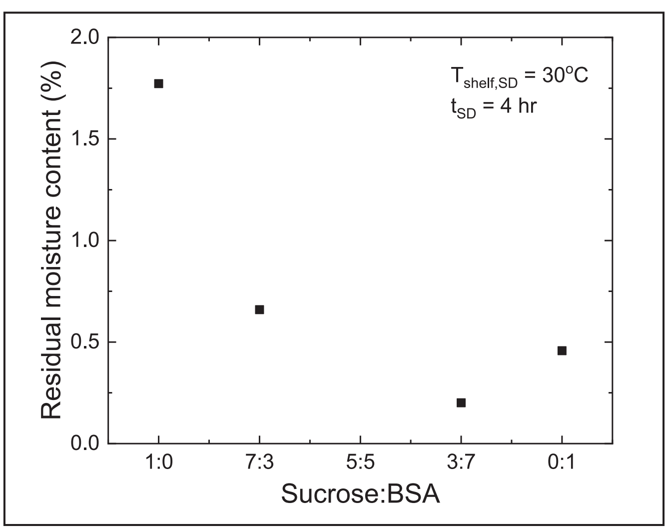

Figure 1: *Residual moisture content (t_{SD} = 4hr) of sucrose/BSA mixtures for different mass ratios of sucrose:BSA.*

References:

[1] Lang, K.W. & Steinberg, M.P. (1980) Calculation of moisture content of a formulated food system to any given water activity, J. Food Sci. 45(5), 1228-1230.

[2] Wang, B., Tchessalov, S., Cicerone M.T., Warne N.W. & Pikal, M.J. (2009) Impact of sucrose level on storage stability of proteins in freeze-dried solids: II. Correlation of aggregation rate with protein structure and molecular mobility, J. Pharm. Sci., 98(9), 3145-3166.

[3] Costantino, H.R., Curley, J.G., Wu, S. & Hsu C.C. (1998) Water sorption behavior of lyophilized protein–sugar systems and implications for solid-state interactions, Int. J. Pharm. 166(2), 211–221.

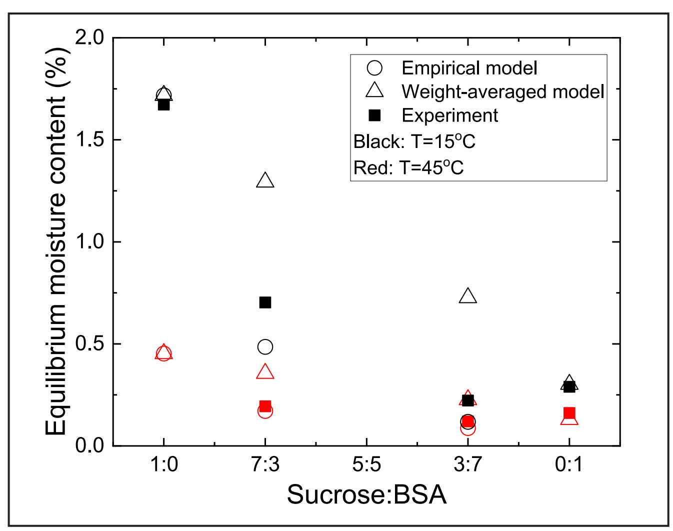

Figure 2: *Measured equilibrium moisture content data versus predicted values using an empirical model (developed in LyoHUB) and a weight-averaged model (linear correlation). Data shows different ratios of sucrose:BSA.*