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Study of the Stochastic Nature of Nucleation in Freeze-Drying

Anna Filčáková¹, Jenny Shepherd², Július Annus¹, Simona Krošláková³, Pavol Rajniak¹

¹Faculty of Chemical and Food Technology STU in Bratislava, Radlinského 9, 812 37 Bratislava

²The University of Leicester, University Road, Leicester, LE1 7RH

³Sitno Pharma, Ltd. Rybné námestie 4135/1, 811 02 Bratislava

anna.filcakova@stuba.sk

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The stochastic nature of nucleation is often considered one of the main limitations of the freeze-drying process, as it introduces unpredictability and variability between samples and within the same batch. The randomness is because ice nucleation – the moment when crystals start to form in a solution – does not always occur at the same temperature or at the same time. The result is differences in the size, shape, and distribution of ice crystals, which in turn determine the microscopic structure of the final product. Samples that start to nucleate earlier (at a higher temperature) tend to form larger ice crystals, resulting in larger pores and lower cake resistance. Conversely, later nucleation leads to smaller crystals and a more compact structure, which slows down sublimation. Variability in nucleation is therefore a critical problem, especially in industries where high reproducibility and quality are required, such as the pharmaceutical, biotechnology, or food industries. However, the underlying mechanism of random nucleation behavior is not yet fully understood, as it depends on several interrelated parameters, such as sample volume, solution composition, and vial placement in the lyophilizer. The results of this study showed that all of these factors contribute to the observed heterogeneity in nucleation.