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EFFECT OF VACUUM INDUCED NUCLEATION ON THE FINAL PRODUCT HOMOGENEITY

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Introduction and aim

In the field of freeze drying of pharmaceutics the homogeneity of the sublimation flux during drying is fundamental to allow a final product with the same characteristics. Previous studies have shown that the control of freezing stage, in addition to a dramatic reduction of cycle duration, can also improve the homogeneity of the final batch. In this framework, this study is focused on the investigation of the effects of the Vacuum Induced Nucleation control method (modified in a previous work)\textsuperscript{[1,2]} on the final structure of the product. Two aspects will be taken into consideration: the uniformity among vials of the same batch (inter-vial) and the uniformity of the structure along the height of the product (intra-vial). It has to be pointed out that a non-uniform product structure can have an impact on the protein aggregation and redistribution, and cause a partial cake collapse or micro-collapse. This investigation is really useful to define some limits of the control method used in this work.

Methods and Results

The first part of the study was dedicated to an inter-vial homogeneity analysis of products produced using both uncontrolled and controlled freezing. In this part, the case studies investigated were batches of vials filled with 5\% (w/w) solutions of mannitol and lactose. The homogeneity of the product was evaluated at the end of the primary drying by comparing the time between the onset and offset of the pressure ratio curves, which was used as an indication of a uniform drying behaviour during drying. To this regard, the results showed narrow time ranges (i.e., more uniform drying) in the case of controlled freezing with respect to conventional freezing (up to 40\% of reduction). On the other hand, it was observed that varying the operating conditions of the control method here used no significant variation occurred. As a further confirmation of the improvement of the inter-vial homogeneity using Vacuum Induced Nucleation, the moisture content at the end of primary drying was also measured (by Karl Fisher analysis) showing more consistent results in the case of controlled freezing (low variance of residual moisture among vials), see Figure 1.

![Figure 1: Distribution of moisture content at the end of the primary drying stage in the case of controlled and uncontrolled freezing.](image)

In the second part of this work the intra-vial homogeneity of the product was taken into consideration. For this purpose, both morphology and product structure were analysed using SEM and XRD analysis respectively and considering a mannitol 5\% (w/w) solution as a case study. Figure 2 shows an example of results concerning the internal product morphology. SEM images shown in the figure regard product obtained with uncontrolled and controlled freezing, changing some parameters of the control method used (i.e., temperature of initial nucleation and holding temperature after freezing induction), and varying filling volume of the solution. As a first assessment it can be noticed a more open
structure in the case of controlled freezing with respect to uncontrolled (Figure 2 a-c), which reflects the shorter primary drying duration found for controlled cycles (low resistance to the vapour flow) by comparing the offset times of the pressure ratio curves. Furthermore, a deeper analysis of the product morphology showed that the application of the Vacuum Induced Nucleation method at high temperatures of initial nucleation and at high filling volumes of the solution had an impact on the uniformity of the morphology along the height of the product. In particular, at temperatures of nucleation higher than -2°C and at filling volumes higher than 4 ml (in the case of: 21 mm internal diameter of vial and -5°C of initial temperature of nucleation) was observed the formation of a thin film of ice at the top of the product, which resulted in the formation of a porous structure at the top of the product and a laminar structure from the middle of the product toward the bottom (see Figure 2 d). This analysis was found useful to define the conditions and the parameters of the Vacuum Induced Nucleation method to be used in order to obtain an homogeneous morphology for the entire product in the vial.

Figure 2: SEM images of a mannitol 5% samples in the case of (a) uncontrolled freezing and freezing induced at (b) -5°C, (c) -10°C, and (d) with high filling volume (5 ml with respect to 3 ml of the other samples).

In addition to the product morphology, the intra-vial homogeneity of the final batch was also tested considering the internal product structure with the use of XRD and RAMAN spectroscopy.[3] The XRD analysis showed a different polymorphs formation depending on both the freezing protocol and the initial temperature of nucleation used. Concerning the RAMAN analysis, it showed that α, β and δ polymorphs were not only freezing-protocol dependent, but also differently distributed within the product. In order to distinguish the various portions of the product and compare different cycle conditions, the cake was cut at different positions (i.e., top, middle and bottom) and RAMAN analysis was carried out comparing polymorphs distribution along each vial, in vials of the same batch, and from different batches. To this regard, a preliminary analysis showed more consistent results in the case of the whole cycles carried out with control during freezing, even if the polymorphs formation changed at different operating conditions of the Vacuum Induced Nucleation method. On the contrary, high variance, in terms of polymorphs formation, was found in the case of uncontrolled cycle, particularly marked in the upper part of the cake. This last information was finally used to discriminate cycles with a prevalent formation of unstable polymorphs that have the tendency to change to another type of polymorph during storage, which is a condition that has to be avoided during a cycle design.

Final conclusions

The control method used in this work was found effective in the improvement of inter-vial homogeneity of the final product of the batch, while an optimal intra-vial homogeneity was obtained by a proper selection of the Vacuum Induced Nucleation parameters. Such a result was confirmed by SEM, XRD, and RAMAN analysis with regard to the internal product morphology and structure, and was confirmed by onset/offset times of the pressure ratio curves and by residual moisture analysis.

The data collected were also used to define the proper filling volume and temperature of initial nucleation to be used in order to improve the intra-vial product homogeneity, while limiting the formation of unstable polymorphs.

Bibliography