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*Original*

Prediction of ice crystal size distribution during freezing of a pharmaceutical solution / Arsiccio, Andrea; Barresi, Antonello; Pisano, Roberto. - ELETTRONICO. - (2017), pp. 1-8. (Intervento presentato al convegno EuroDrying'2017 – 6th European Drying Conference tenutosi a Liège, Belgium nel June 19-21, 2017).

*Availability:*

This version is available at: 11583/2683386 since: 2018-08-09T19:50:11Z

*Publisher:*

University of Liège

*Published*

DOI:

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## PREDICTION OF ICE CRYSTAL SIZE DISTRIBUTION DURING FREEZING OF A PHARMACEUTICAL SOLUTION

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**Abstract:** In this work, we develop a mathematical model that allows the prediction of the crystal size distribution of ice over the entire height of products frozen in vials. Unlike previous approaches, which were all based on empirical observations, all the terms used in the model here presented have a clear physical meaning. The model predictions have been validated using experimental data collected analyzing with SEM microscopy the pore dimension of freeze-dried products.

**Keywords:** freezing, crystal sizing, mathematical modeling, freeze-drying, pharmaceutical solutions

### **Introduction**

Prediction of the crystal size of ice in frozen products is a major issue in several fields of technology and would prove beneficial for food, chemicals, and pharmaceutical industries. For example, the ice crystal dimension of products to be freeze-dried is a critical aspect [1].

As a consequence of the importance of the subject, many research works have been developed to obtain a quantitative relationship that correlates the thermal history with the size of the ice crystals, but these are all empirical formulas and lack of physical explanation [2,3,4]. Moreover, all the equations proposed so far have a restricted field of application.

The aim of this work is the development of a mathematical model capable to provide physical insight into the process and to predict the ice crystal size distribution in wide ranges of conditions.

### **Mathematical formulation**

We applied a heat balance to the crystallization zone. We supposed that in this zone the heat generated by the crystallization of ice is completely compensated by the heat removed by the external environment and by the energy requested for generation of a new solid-solid interface. We also imposed the respect of the mass balance and found a relationship between the number and the dimension of ice crystals.

Using these equations, a general model was developed which is valid over a wide range of conditions; however, by making some simplifications to the heat balance, we found a simpler model valid for dilute solutions.

### **Materials and Methods**

The formulations investigated in this work were mannitol or sucrose solutions at different concentrations. Each solution was freeze-dried and the pore dimension of the freeze-dried product, which corresponds to the ice crystal size of the frozen product, was determined using Scanning Electron Microscopy (SEM).

The temperature profiles during freezing, required for the application of the model, were obtained from numerical simulations of the freezing step, performed using the commercial CFD software COMSOL Multiphysics.

## Results and discussion

The model has proved to be valid for different operating conditions and for different freezing protocols. Moreover it has been demonstrated to correctly predict the ice crystal size for both crystalline (e.g. mannitol) and amorphous (e.g. sucrose) formulations (Fig. 1).

Finally, the validity range of the simplified model has been experimentally determined.

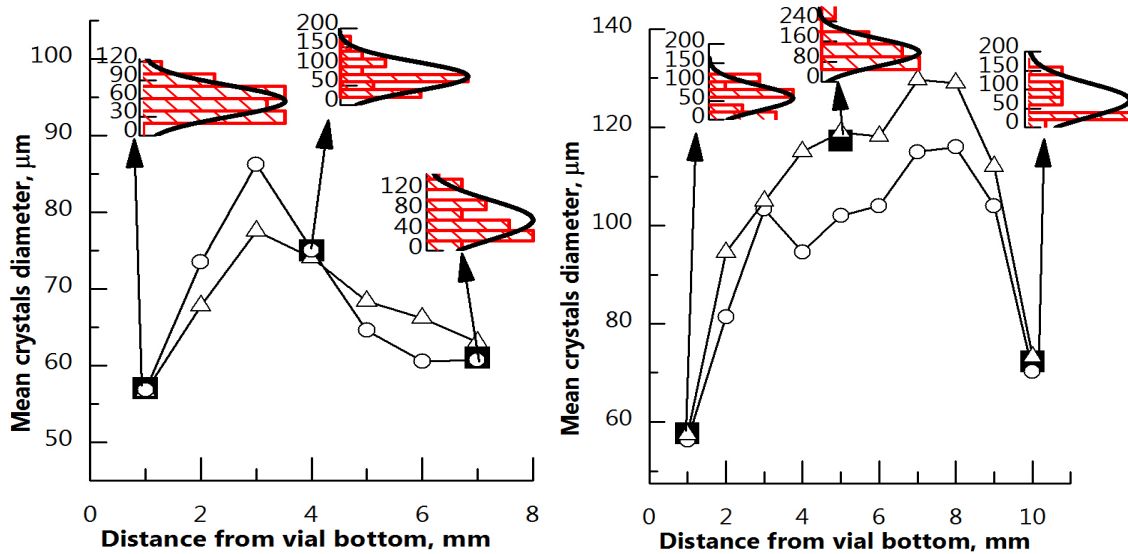


Fig.1. Comparison of ice crystal mean size obtained by SEM analysis (■) and predicted by the general model (-Δ-) and the simplified model (-O-). The histograms refer to the ice crystal size radial distribution observed with the SEM analysis. Left: mannitol solution. Right: sucrose solution.

## Conclusions

We developed a general model and a simplified model, valid for dilute solutions, capable to predict the ice crystal dimension of products frozen in vials, which is a critical parameter of the freeze-drying process.

Unlike previous approaches, all the terms of our model have a strong physical meaning and a clear explanation. Moreover, the field of application of the model presented is much wider than that for correlations proposed so far. Thus, this work represents a significant progress towards the possibility to "choose" in advance the crystal structure of the final product.

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