Authors: **T.Vandeputte**[1,2], M. Ghijs[1,2], M. Vandromme, S. Van Langenhove, T. De Beer[2], I. Nopens[1]

(1)BIOMATH, Ghent University, Ghent, Belgium

(2)Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ghent, Belgium

Title: **Clarifying the formulation effect on the drying behavior of pharmaceutical granules after wet granulation**

Abstract:

Pharmaceutical (wet) granulation aims to reduce the effect of the initial powder properties and replace them with the enhanced granule properties, this in order to enable downstream processing and tableting. The question remains as to which degree the initial properties of the active pharmaceutical ingredient (API) affect the process behavior in the subsequent fluid bed drying stage. This is important knowledge for the mechanistic modeling of this complex process: this constitutes whether any drying model should include the effect of API properties on the evaporation of the remaining water from the granules. This is a pivotal stepstone in the development of a generic drying model, which predicts drying behavior in function of formulation properties.

The goal of this work is therefore to quantify the influence of the API properties on the general drying behavior of granules, present in a fluid bed dryer of a continuous wet granulation line for pharmaceutical tablet production. This research was conducted using a ConsiGma-25™ semi-continuous fluid bed dryer (GEA), which is fed with wet granules from a twin-screw granulator through pneumatic transport in a tube. This dryer is characterized by six separate drying cells over which the continuous flow of wet granules is divided. A sequential filling pattern and parallel drying cycles allow this dryer to handle the continuous inflow. The key product, being the amount of granules that was loaded into a cell, subsequently is dried in this cell and discharged all at once downstream, where the continuous material stream is restored.

Recently, a new mechanistic multi-level model for this drying system was developed within our research group, starting from several previously described drying models. Each model describes the drying behavior on a different level. The population balance model (PBM) described by Peglow et al [1] was used as the base to describe the evolution of the drying air conditions in the drying cell such as the wall temperature, the air temperature, and the relative air humidity according to the bed height, assuming a bubbling fluidization regime. This is considered to be the bulk level of the model. This basic structure was then complemented with the single particle drying model described by Mortier et al [2] to obtain more accurate predictions of the granular drying behavior, such as the dynamics in granule temperature and the residual moisture content. This constitutes the drying behavior on a granular level. Besides that, this model was extended in order for it to simulate a continuous granule inflow and predict the drying behavior of wide granule size distributions. This multi-level drying model was validated for two different formulations from which it was concluded that the obtained model has a sufficient amount of predictive power for those APIs.

This study is the next building block for making the model generic for API properties, such as solubility, hydrophilicity, or grade. This thus leads to the API-level component in the modelling of drying behavior. To extend the existing mechanistic multi-level drying model, a relevance study on the influence of API properties on the overall drying behavior is performed. It is, however, important to make the trade-off between the additional required computing power and the increased accuracy of the predictions when an extra level is added to an existing model structure. In this experimental study, two different formulations with different API properties were granulated in such a way that

comparable granules were obtained, considering the size distribution, the porosity, and the initial moisture content. Additionally, an extra API grade of one of the previously mentioned formulations was also included to account for API powder size. The dosages of the API were high, constituting 50 wt% of the formulation.

In total, six different drying experiments, supplemented by three repeated center point experiments, were performed on the similar granulates of each formulation under investigation. In this study, three different comparison points related to the granule properties were included. Complemented by varying the inlet air temperature between 40 and 60°C and the filling time, governing the cell load, between 90 and 180s. Each experimental point was conducted for, at least, three different drying times, ranging from 10 seconds added to the filling time to maximally two and a half times the filling time. The high-resolution PSD of the dried granules was collected using a particle size analyzer, QICPIC (Sympatec), with a dispensing system, Gradis (Sympatec). The residual moisture content is measured by a NIR-Cl camera system, according to the method described in Ghijs et al. [3].

One of the most important conclusions following from the newly gathered data are the different breakage patterns, due to the fluidization process and/or pneumatic transport, for similar granules prepared with different formulations. This observation implies that the present granule size distribution, after certain drying times, differs according to the formulation properties. It is obvious that the granule size has a major influence on the evaporation rate and consequently the drying behavior.

From this perspective, it is useful to include this additional level, which considers the formulation properties, in the multi-level mechanistic fluid bed drying model. A comprehensive and accurate mechanistic drying model constitutes an important step towards generic models, that can be utilized for model-based process analysis or process control of continuous manufacturing in the pharmaceutical industry. More importantly, the generic model should be able to predict the drying behavior for new APIs where data on manufacturing is scarce. Such models are thus essential to facilitate the industry's transition to continuous manufacturing of pharmaceutical tablets and the effect of API in the drying behavior is an important factor in this.

References:

[1] Peglow, M., Kumar, J., Heinrich, S., Warnecke, G., Tsotsas, E., Mörl, L., & Wolf, B. (2007). A generic population balance model for simultaneous agglomeration and drying in fluidized beds. *Chemical Engineering Science,* 62(1-2), 513-532.

[2] Mortier, S. T. F. C., De Beer, T., Gernaey, K. V., Vercruysse, J., Fonteyne, M., Remon, J. P., Vervaet, C., Nopens, I. (2012). Mechanistic modelling of the drying behaviour of single pharmaceutical granules. *European Journal of Pharmaceutics and Biopharmaceutics*, Vol. 80(3), 682–689

[3] Ghijs, M., Vanbillemont, B., Nicolaï, N., De Beer, T., & Nopens, I. (2021). Two-dimensional moisture content and size measurement of pharmaceutical granules after fluid bed drying using near-infrared chemical imaging. *International journal of pharmaceutics,* 595.