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Scenario Analysis on a PBM describing the drying behaviour of wet pharmaceutical granules

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1 Introduction

For the production of pharmaceutical tablets, a drying step is performed when a wet granulation technique is used as preceding step. Fluidized beds are often used for the drying of these wet granules. The choice of the drying technique and drying process settings is important as it may influence the resulting properties of the granules and tablets[1]. Due to the trend to move towards continuous production processes the necessity to develop mechanistic process knowledge through modelling is emerging. These models can help to understand processes in more detail, and in the end they can be used for process control. Process knowledge can be gathered by studying input-output relations. Mechanistic models are helpful to detect input variables which have a significant impact on the process.

The case under study is a fluidized bed drying system which is part of a full continuous from-powder-to-tablet manufacturing line (ConsiGma$^{\text{TM}}$, Collette$^{\text{TM}}$, GEA Pharma Systems). The drying system consists of six segments, which are fed consecutively with continuously produced wet granules, hence allowing continuous drying.

A model describing the drying behaviour of single pharmaceutical granules was developed previously[2]. This model was calibrated and validated using experimental data, after which a model reduction was performed resulting in an empirical reduced model. This step was necessary in order to allow incorporation in a Population Balance Model (PBM).

The PBM is able to describe the drying behaviour for a batch of granules for different values of the gas temperature of the drying air (T_g), the particle radius (R_p), the gas velocity (V_g), the initial moisture content of the particles ($R_{w,0,fac}$), the filling time (t_{fil}) and the drying time (t_{dry}). The objective of the work presented here is to investigate the influence of the change in gas temperature and gas velocity over time on the distribution of the residual moisture content at the end of the drying process. The latter is important since it influences the quality of the product.

2 Materials and methods

2.1 Reduced drying model

The reduced model for the drying of a single granule at different gas temperatures was described in detail by Mortier et al.[3]. An extension for the first drying phase was made to include the dependency on the gas velocity. The empirical equation for the first drying phase was determined to be:

$$G^*_{r,1}(R_{w,nor}, T_g, V_g) = (v_1 \cdot V_g^2 + v_2 \cdot V_g + v_3)\, G_{r,1}(R_{w,nor}, T_g) \tag{1}$$

$$G_{r,1}(R_{w,nor}, T_g) = A + B \cdot R_{w,nor} + C \cdot e^{D \cdot R_{w,nor}} \tag{2}$$

$$R_{w,nor} = \frac{R_w - R_p}{R_{w,0} - R_p} \tag{3}$$

where v_1, v_2 and v_3 are empirical coefficients, A, B, C and D are empirical coefficients, which are dependent on T_g, and $R_{w,0}$ is the initial (wet) radius[3]. The behaviour of the second drying phase is described by:

$$G_{r,2}(R'_{w,nor}, T_g) = A' \cdot (R'_{w,nor})^{B'} + C' \cdot \left(1 + D' \cdot R'_{w,nor}\right)^{E'} + R'_f * (A' \cdot 0.5^{B'} + C' \cdot (1 + D' \cdot 0.5)^{E'}) \tag{4}$$

$$R'_{w,nor} = \frac{R_w}{R_p} \tag{5}$$

with A', B', C', D' and R'_f empirical coefficients, dependent on T_g[3].

2.2 Method of Characteristics (MOC)

The Method of Characteristics (MOC), which uses a moving grid, is used to solve the PBM[4]. This solution method gave the best results taking both the accuracy and computational load into account[5]. A grid size of 150 was used for the calculations. A grid independency check was performed earlier[5].

2.3 Different scenarios

Different scenarios were tested, where the gas temperature and gas velocity are changing over time mimicking the varying local T_g and V_g values the particle encounters when travelling through the fluidized bed (Table 1). The input is artificially created while awaiting results from a Computational Fluid Dynamics (CFD)-model of the fluidized bed. The idea is to investigate the impact of fluctuating conditions on the characteristics of the distribution. For most scenarios T_g decreases at the start, which is reasonable as T_g in the fluidized bed will decrease due to the heat needed for evaporation of water. Other scenarios that are studied are the impact of a constant value for T_g (scenario 3), a higher initial value for T_g (scenario 4) and a faster decrease and increase of T_g (scenario 6). The effect of the V_g is investigated using a sinusoidal behaviour, where the mean (scenario 5) and the frequency (scenario 7) of the oscillation is varied. The comparison with a constant value (scenario 2) is also studied.

In figure 1 the input for the gas temperature and gas velocity is presented for the different scenarios.

Table 1: Definition of the different scenarios

Scenario	T_g	V_g
1	Start: 40 °C - Decreasing till 600 s - Increasing till the end	Sinusoidal behaviour around 300 m^3/h
2	Start: 40 °C - Decreasing till 600 s - Increasing till the end	Constant at 300 m^3/h
3	Constant at 40 °C	Sinusoidal behaviour around 300 m^3/h
4	Start: 50 °C - Decreasing till 600 s - Increasing till the end	Sinusoidal behaviour around 300 m^3/h
5	Start: 40 °C - Decreasing till 600 s - Increasing till the end	Sinusoidal behaviour around 350 m^3/h
6	Start: 40 °C - Decreasing faster (till 200 s) - - Increasing till 40 °C	Sinusoidal behaviour around 300 m^3/h
7	Start: 40 °C - Decreasing till 600 s- Increasing till the end	Faster sinusoidal behaviour around 300 m^3/h

3 Results

In figure 2 and figure 3 the evolution of respectively the mean and the standard deviation of the distribution of the moisture content in time in the dryer is presented for the different scenarios. A higher value for T_g increases the evaporation rate and as such the moisture content decreases faster (scenario 4). A constant value for T_g also benefits the drying rate (scenario 3). However, in both cases the standard deviation of the resulting distribution

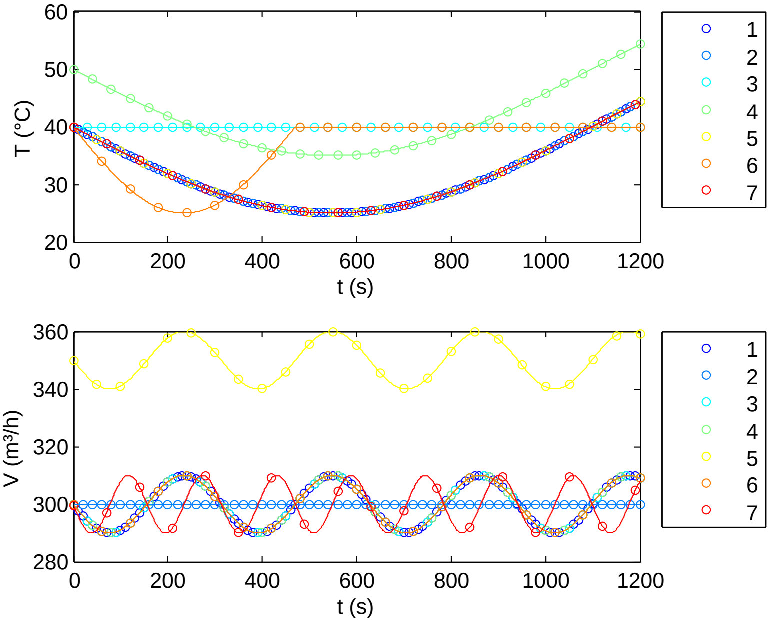

Figure 1: Gas temperature and gas velocity for the different scenarios

is larger, meaning that some particles are considerably more dry compared to others which is undesired. A T_g increase of 10 °C increases the standard deviation enormously (scenario 4) over the whole time range. When a constant value for T_g is used, the width of the distribution decreases again (scenario 3). When the decrease in T_g is faster (scenario 6), the moisture content is higher in the beginning of the drying process compared to the other scenarios, but is significantly lower at the end. It is obvious that the standard deviation is lower for this scenario. Both at the start and at the end of the drying phase the moisture content is more identical for the different granules in the batch.

Focusing on the effect of the V_g, almost no difference can be detected in the mean and the standard deviation of the distribution of the moisture content. The gas velocity only has an influence on the first drying period, as V_g is not involved in the equation for the second drying phase (Equation 4).

4 Conclusions

The gas temperature of the drying agent clearly has an influence on the drying behaviour of wet granules. A high value for T_g is interesting to increase the evaporation rate, but is unfavourable when a narrow inter-granule residual moisture distribution is desired. On the other hand the gas velocity has almost no influence on the moisture content distribution and is not very useful as a control handle. These preliminary results indicate that a controlled T_g is the key to control the specs of the moisture content distribution at the outlet of the dryer.

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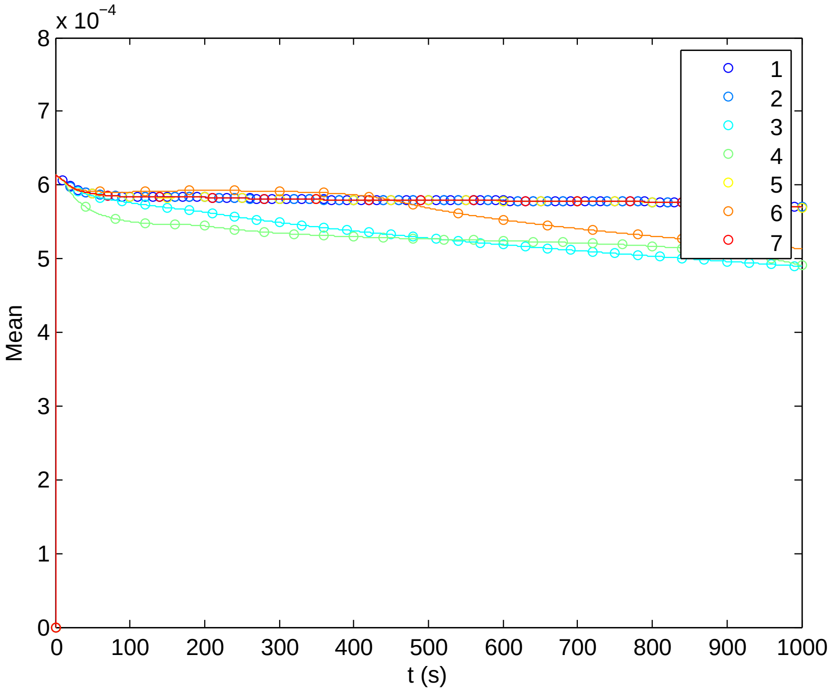

Figure 2: Evolution of the mean (%) of the distribution for the different scenarios

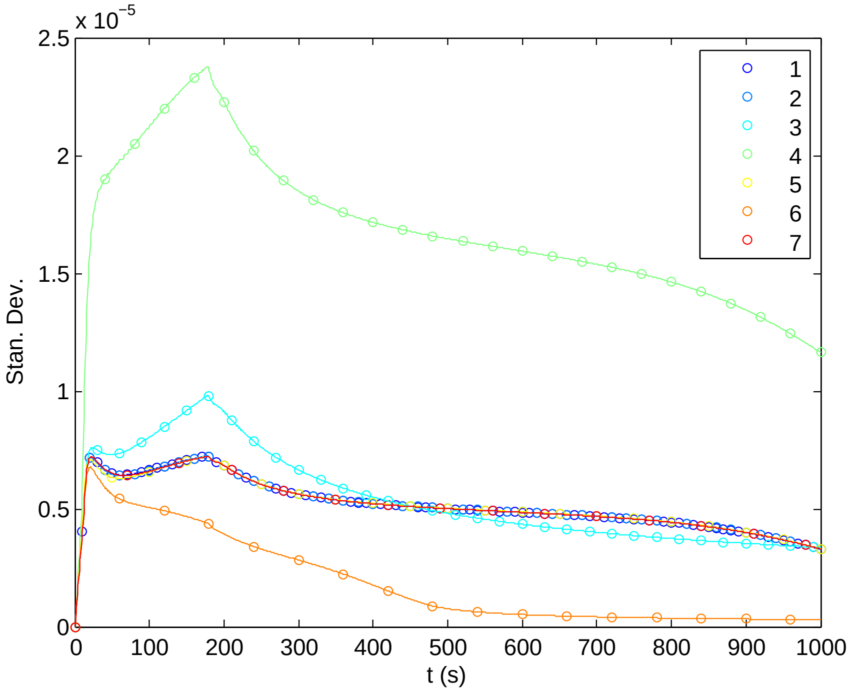

Figure 3: Evolution of the standard deviation of the distribution for the different scenarios