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Process Simulation of Fluidized Bed Granulation: Effect of Process Parameters on Granule Size Distribution

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The purpose of granulation is to improve the flowability of powders, whilst reducing the dustiness and potential of segregation. The focus of this project is to understand the effects of the process parameters of fluidized bed granulation on the granule size distribution of the final product using gFP simulation software (Siemens PSE, UK). The wet granulation process has become predominant and important in the pharmaceutical industry, due to its cost-effectiveness and its robustness in product formulation. The process parameters that were subject of this study include the air flow rate of 20, 40 and 60 m3/hr., the binder concentration of 6, 9 and 12 wt.%, and the binder spray rate of 7.14, 14.28 and 21.42 ml/min. The results show that binder spray rate has the most impact on the granule size distribution, where an increase in binder spray rate is associated with a higher incidence of larger granules in the product. The air flow rate and the binder concentration have a negligible impact on the granule size distribution when agglomeration and consolidation models are not implemented in the simulation.

1. Introduction

Granulation is defined as the formation of a larger permanent mass of particles through combining smaller particles such that the composition of the individual particles is not destroyed. There are two significant classifications of granulation, wet and dry granulation (Ennis and Litster, 1997). Wet granulation has been identified with two main liquid addition and the agitation process. The fluid addition process promotes nucleation and coalescence by adding binder liquid to the powder, whilst the agitation process stimulates material mixing, distribution of liquid, and granule growth (Iveson et al., 2001). The objective of granulation is to prevent the segregation of powder mixture and improve powders' dissolution rate. It also helps enhance powder flowability, reduce dustiness, and improve powder handling and product formation. Manufacturing industries employ the granulation technique in the production of fertilisers, food, plastics, pharmaceutical tabletting, and agrochemicals (Rahmanian et al., 2011). Fluidized Bed Granulation is a prevalent granulation technology in the pharmaceutical industry. It is a multi-functional system that can perform granulation, mixing and drying in the same unit. The system consists of an inlet gas chamber, the gas distribution section, a product container, and the expansion chamber, which contains a set of filter bags, and binder spray nozzles (Muddu et al., 2018). The presence of these parts is subject to the processing option, principle and mode of operation and equipment used. The main principle behind fluidised bed granulation is the powder bed's suspension and the binder's spraying onto the powder either below or above (Becher and Schlünder, 1997). The challenges associated with FBG include uniform densification, longer residence time, higher amount of granulation liquid needed, and its relative higher acquisition cost. The positive aspects that make the FBG a viable granulation system in the pharmaceutical industries include the comparatively more remarkable heat transfer ability for drying and drying products uniformly, which prevents mottling is generally used in the pharmaceutical industry to produce solid dosage drugs, enhancing the compaction and flowability of the powder.
In this paper, gPROMS simulation software developed by PSE (Danish et al., 2021) would be utilised to investigate the effect of binder liquid concentration, spray rate and volume on the particle size distribution. (Suresh et al., 2020) performed an experimental study on FBG using Lactose Monohydrate. Polyvinylpyrrolidone (PVP) and Microcrystalline Cellulose (MCC) as the feed powder and liquid binder, respectively. The parameters

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set for this model simulation is based on the experimental investigation from (Suresh et al., 2020) and serve as the validation for the resulting data from the simulation. This paper seeks to highlight the importance of aggregation and consolidation Kernel in modelling and simulation of granulation rate process as they form the dominant rate process in granulation (Paavola et al., 2013)

2. Methodology

2.1 Design of simulation

In this research, a total of 27 experimental simulations were conducted using gPROMS Formulated Product 2.0 (gFP) software. These consist of three different air volumetric flow rates, three different binder volumetric spray rates and three different binder concentrations. Lactose monohydrate and Avicel powder are the granulation powders, and a solution of water and HPMC is the liquid binder.
In this research, the influence of agglomeration, and consolidation Kernel are analysed. In determining the effect of liquid binder and air flow rate on the final granule size in fluidized bed granulation, two different sets of simulation were undertaken. In the first simulation the aggregation and consolidation Kernels were not factored into the simulation and the second set of simulations had aggregation and consolidation factored in (Sayin, 2016). The kinetic model for layering (Sayin, 2016) was implemented. The nucleation model was chosen based on the work of (Hapgood et al., 2009). The drying model for heat and mass transfer was selected based on (Burgschweiger and Tsotsas, 2002) models. The model design of the fluidised bed granulator used in this simulation had a volume of 0.25m^3 with a cross-sectional area of 0.117m^2. The wall heat transfer coefficient was set at 38.5 $Wm^{-2}K^{-1}$ with an ambient temperature of 20°C. The spraying angle was 60° and the distance between the bed and nozzle was 10cm. These were set to match Suresh et al (2020) experimental setup.

2.2 Flowsheet of the granulation process

Figure 1 shows the flowsheet of FBG in the gFP environment. The initial conditions set for this simulation include the FBG containing some granulating materials and an initial material temperature of 25°C. There is a liquid source that contains the biner liquid. The liquid is introduced into the FBG at a specific spray rate and concentration. The vapour source has air made up of 79% Nitrogen and 21% Oxygen at a temperature of 85°C to ensure complete drying of the final products. The air is introduced into the system at a specified constant flow rate. The flow profile of the piecewise constant was selected with three intervals for bed fluidisation (8 mins), binder addition (5 mins) and granule drying (17 mins). The simulation was run for 30 minutes.

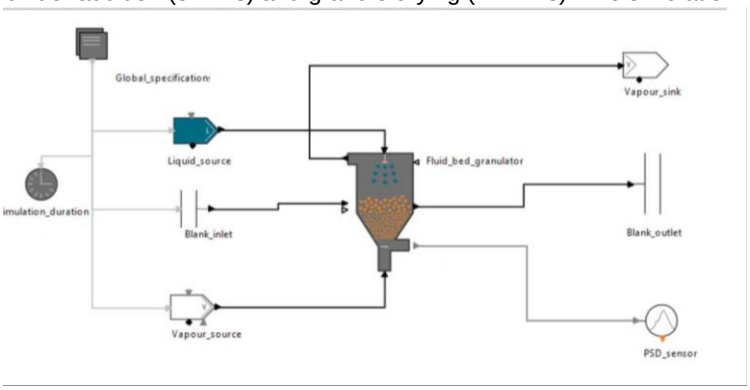

Figure 1 The process flowsheet of FBG process in the gFP simulation.

3. Results and discussion

Suresh et. al., 2020) have shown in their experiment on fluidised bed granulation that the variation in the volumetric flow rate of drying air, binder liquid spray rate and binder concentration influence the PSD. In this paper, the data from the simulation of this variation will be presented and discussed. There is also an attempt to compare and verify the data from simulation with the previous experimental works.

3.1 Effect of binder concentration (without agglomeration and consolidation Kernel)

Table 1 illustrates the mean particle size and Sauter mean for the three different binder concentrations at three binder spray rates under the constant airflow rate of 20m^3/hr. There is an increase in the average granule by 24.02% and 43.12% when the binder spray rate increased from 7.14ml/hr to 14.28ml/hr and from 7.14ml/hr to 21.42ml/hr, respectively. Table 1 indicates that the change in binder concentration does not affect particle size distribution.

Table 1 Average particle size at 20m/hr air flow rate.

Air vol. flow rate (m^3/hr)	Binder spray rate (mL/min)	Binder conc. (wt.%)	Average granule size	%Change [average granule size	Sauter mean granule size (µm)
20	7.14	6	150.4	0.00	123.6
20	7.14	9	150.4	0.00	123.6
20	7.14	12	150.4	0.00	123.6
20	14.28	6	187.0	24	154.8
20	14.28	9	187.0	24	154.8
20	14.28	12	187.0	24	154.8
20	21.42	6	215.4	43.2	180
20	21.42	9	215.4	43.2	180
20	21.42	12	215.4	43.2	180

The plot in Figure 2 indicates that the binder concentration of 6wt%, 9wt%, and 12wt% all had the same PDD (volume basis). These suggest that this range of binder concentration had minimal effect on the particle distribution in the simulation. From Table 1, there was no change in the mean particle size for the three varying binder concentrations when the binder flow rate was 7.14mL/min, with 0.02µm change in the mean particle size and 0.4µm change in the mean particle size under the air flow rate of 14.28mL/min and 21.42mL/min, respectively for the various binder concentration. The particle size remains the same irrespective of the binder concentration. When comparing the experimental results from (Suresh et al., 2020), a binder flow rate of 7mL/min indicates an increase in the mean granule from 6.6% to 18% when the binder concentration was increased from 5.9wt% to 8.6wt% and subsequently to 11.1wt% respectively. This increase suggests that an increase in binder concentration has a corresponding increase in the mean granule size. This finding is contrary to the results from this simulation. Also, the experiment's average particle size (between 213.4µm and 251.9µm) under the same process and formulation parameters are much higher than the average particle size (150.4µm**)** obtained from the simulation. This non-correlation between the experimental and simulation data may be attributed to the non-inclusion of agglomeration and breakage models.

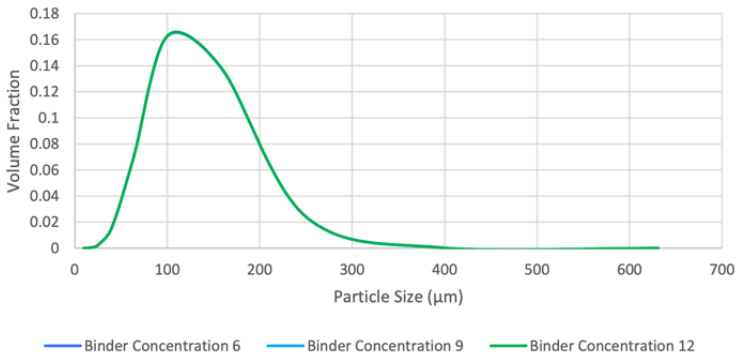

Figure 2 PSD at varying binder concentration (without consolidation and agglomeration Kernel).

The exclusion of the agglomeration Kernel from the initial simulation indicates that the description of the granule formation at the nuclei-particle level has been omitted from the process. This gives rise to the simulation not properly accounting for the impact of the binder concentration and volume on the granule sizes produced. Although the nucleation Kernel will indicate the size and number of nuclei produced at any given volume and concentration of binder solution in a mass of mass granulating powder, but the agglomeration Kernel is needed to describe the onward process of the nucleus to nucleus and particles to nucleus bonding to forming larger granule size. It is at the agglomeration level that the true impact of binder concentration and volume could be experienced. Thus, the non-prediction of the effect of binder concentration on granule size is seen in Figure 2. There is a corresponding increase in granule size with increasing binder volume as seen in Table 1, this is expected as increasing binder volume increases the binder droplet size and number which tends to increase the size of nuclei produced thus larger granule size. The predicted granule size, in this case, is still smaller than experimental values even with consolidation still not accounted for.

3.2 Effect of binder concentration with consolidation and agglomeration Kernel

By implementing the (Rajniak P et al., 2016) as the agglomeration model, and (Barrasso et al., 2015) and (Bellinghausen et al., 2022) as consolidation model in the simulation the following results were obtained. The simulations at constant binder flow rate of 7.14mL/min, air flowrate of 20m3/hr and varying the binder concentration between 6, 9, and 12wt% show a deviation from the initial simulation when the agglomeration and consolidation models had not been implemented. The implementation of agglomeration model has factored in the bonding activities of nuclei to particle and nuclei to nuclei causing an increase in the mean granule size to be around 200μm with a higher volume fraction as compared to 100μm in Figure 2. With the implementation of the growth models the effect of the binder concentration could be predicted. From Figure 3 it could be deduced that higher binder concentration tends to increase granule size. This is due the ability of higher concentrations of binders having higher bonding forces thus causing greater number of bonding particles to be bonded together to form a larger size. The forces of attraction between bonding particles are greater at higher concentration thus, being difficult to break into smaller pieces during breakage. It should be noted that, the growth models are functions of viscosity (also a function of concentration) and volume and are directly proportional to growth rates.

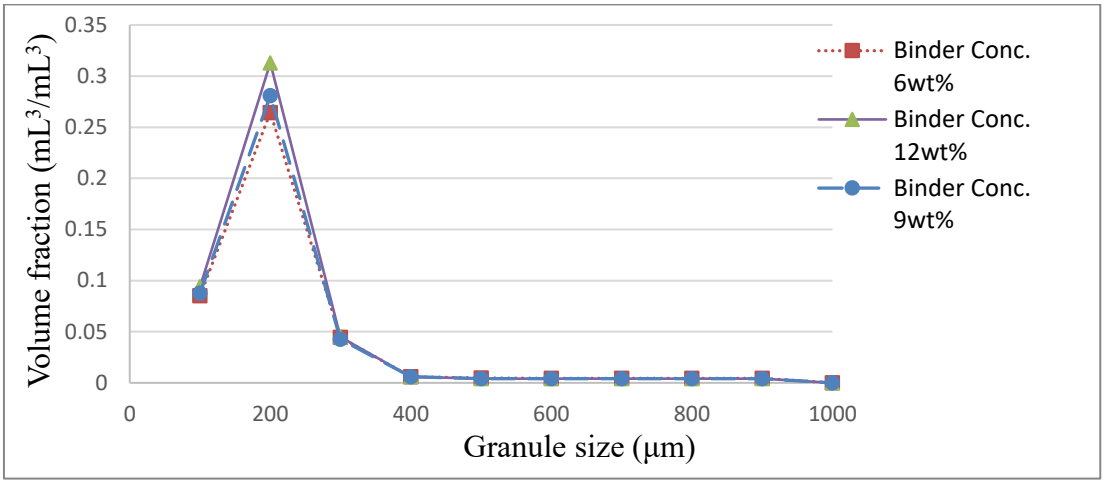

Figure 3 Effect of binder concentration on granule Size distribution (with consolidation and agglomeration Kernel)

3.3 Impact of binder volumetric flow rate with consolidation and agglomeration Kernel

From Table 1 and Figure 4, increasing binder flow rate increases the mean granule size. This result is expected as an increase in the amount of the binder liquid increases the number of nuclei produced during nucleation. This increases the number of bonding surfaces as powder surfaces get into contacted with the binder liquid thus reducing the surface area of the powders hence encouraging bonding activities. As more powder surface gets in contact with liquid through a higher volumetric flow rate, the consolidation rate increases as the liquid binder enters the pores medium replacing gases more faster helping in the distribution and mixing of the binder for it adhesive function. The implementation of the aggregation and consolidation Kernel factored in this simulation helped in analysing the influence of the binder flow rate on granule size.

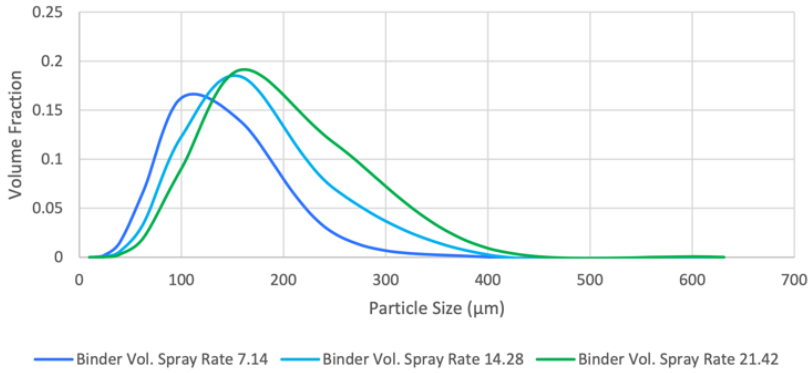

Figure 4 Volume fraction for different binder flow rates.

3.4 Effect of flow rate of fluidized air (without agglomeration and coalescence Kernel)

Figure 5 shows the volume fraction against particle size distribution at a constant binder concentration and binder flow rate under various fluidised air flow rates. Without the implementation of the coalescence model and aggregation models in these simulations, it is observed that an increase in the fluidised air flow rate did not affect the granule size distribution. Increasing fluidised air flow rate is thought to improve how particles collide with each other. In ideal situation, increasing the fluidized air flow rate should cause an increase in the agglomeration rate thus increasing granule sizes. Also, increased fluidized air flow should tend to increase the action of consolidation and coalescence. This is because, increased fluidised air causes particles to move faster in bonding process thus facilitating the driving out of air from pole spaces faster under the action of coalescence and consolidation. Figure 5 indicates that, without the implementation of these appropriate models of granulation rate processes which are essential for fluidized bed granulation, the appropriate effect of fluidized air flow on granule size distribution cannot be predicted correctly.

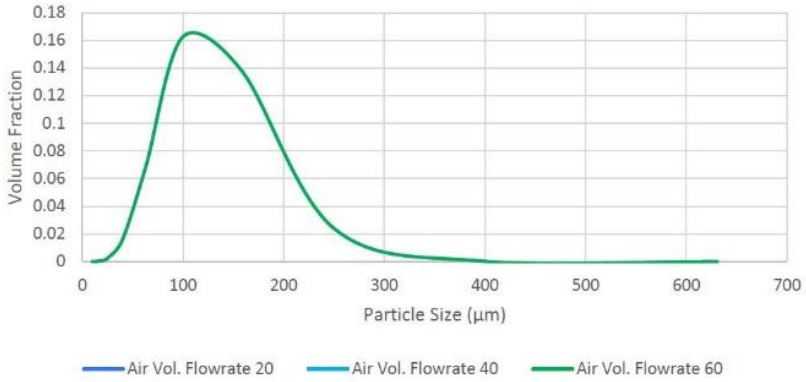

Figure 5 Effect of Air Fluidised Flow Rate (without agglomeration and coalescence model) on PSD.

The comparison between different simulation conditions and those from the literature is represented in Figure 6. It is observed that when the binder concentration is increased, there is a corresponding increase in the average granule size. Also, its corresponding increase in binder flow rate relatively increases the average particle size as shown in the literature (Suresh et al., 2020). For simulations where agglomeration and consolidation models were not implemented, an increase in the binder concentration did not affect the mean particle size. Although an increase in the binder flow rate increased the mean particle size, the simulations with agglomeration and consolidation models being implemented had a more significant increase in the mean particle size relative to simulations without agglomeration and consolidation models. Also, the simulations with agglomeration and consolidation models increased the granule mean size when binder concentration is increased. The results from experimental literature have greater mean granule size compared to simulated data although, implementing agglomeration and consolidation models in the simulation produces results that follow the same pattern as results from the literature. The results from simulation are not expected to be the same as the results from the experimental data but should be close and follow the same pattern as results from the investigation.

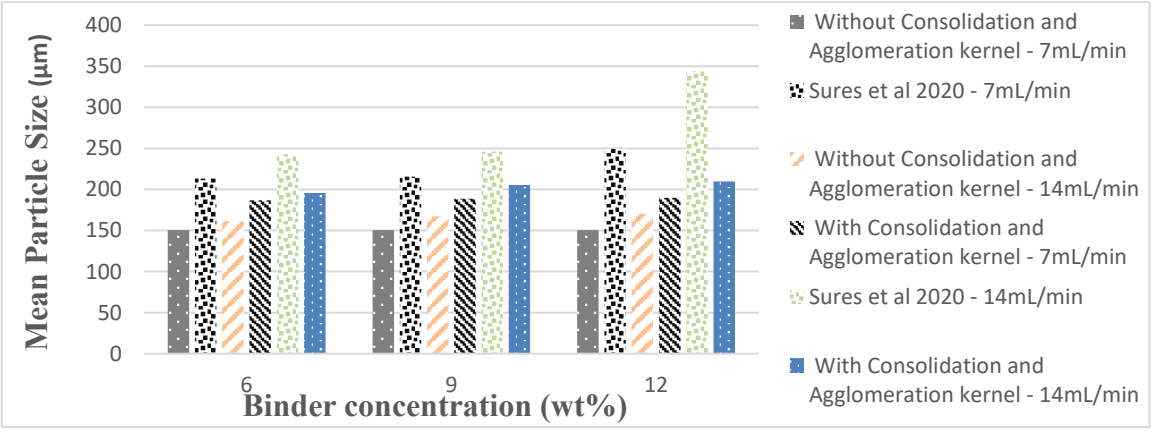

Figure 6 The mean Particle size from the simulation against the data from the literature.

4. Conclusion

Process simulation of FBG was conducted using the latest version of gFP software (2.1). The data from (Suresh et al., 2020) has been used to validate the model. The results from the simulations and literature indicate that increasing binder concentration and binder flow rate turns to increase the average granule size distribution, whereas increasing the fluidised air flow rate turns to reduce the mean granule size. In other words, the trends of obtaining results from this study is matched with those from the literature (Suresh et al. 2020), however the exact values are not the same. This indicates that there is a need to investigate to find impact of other agglomeration and consolidation models in the simulation designs for accurate simulation results. The importance of agglomeration and consolidation/coalescence in fluidized bed granulation has been analysed and it is recommended that in the simulation of the impact of formulation and process parameters on granule size distribution and other granule physiology, the consolidation and aggregations Kernels need to be included and are prerequisite. It is recommended that various consolidation and agglomeration Kernels investigate a precise model for fluidised bed granulation. Also, simulations should include breakage models. The results from both the literature and this simulation shows that under the stated range of process, formulation, design parameters, powder and binder properties, the granule size distribution falls between 100 and 400µm with peaks values between 150µm and 300µm.

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