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DRYING IN A CONTINUOUS WET GRANULATION LINE: INVESTIGATION OF DIFFERENT END OF DRYING CONTROL METHODS

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ABSTRACT

Continuous manufacturing in the pharmaceutical industry has been gaining traction in the past few years. To fully understand and optimise continuous manufacturing processes it is important not only to focus on the single units which act as building blocks but also to understand how the parameters in different units affect and interact each other and the final product. In this study, the drying behaviour of granules in a segmented fluidised bed dryer was studied. Granules were produced in a twin screw granulator, forming part of a continuous powder to table line (Consigma-25). The temperature readings and the moisture content were recorded during the drying process of granules produced with different amounts of liquid binder. From the temperature profiles, it was possible to create a method able to detect when the drying process loses efficiency (the drying rate drops) and therefore predict the optimal drying time at different conditions. The method was validated via online Near Infra Red (NIR) moisture measurements to detect the moisture content of the granules during

the drying, and was compared to the available fixed drying time and temperature controlled end of drying methods. The method was successful in targeting a specific moisture content and could be used to locate the optimal drying temperature for a target moisture content in the future. The moisture content during the filling of the dryer was also recorded and provided further insight into the drying behaviour of the granules in the segmented dryer; this characteristic behaviour could later be used to detect problems during the filling time. The drying rate was also calculated making it possible to predict the optimal drying time at different operating conditions in the granulator and to assess the impact on drying of the different liquid to solid ratio used.

KEYWORDS

Continuous manufacturing, drying, fluidised bed, Consigma-25.

1. INTRODUCTION

In the past few years the pharmaceutical industry has been moving from batch to continuous manufacturing, this change has been pushed by the increase in competition, decrease in profit margin and by the push of various regulatory bodies such as the Food and Drug Administration (FDA) on quality by design and continuous manufacturing [1]. Continuous manufacturing has several advantages such as faster product development, lower waste production, higher energy efficiency, smaller production facilities and the ability to control the product quality during the process [2]. Continuous manufacturing has also presented both formulation scientists and equipment designing companies with new challenges. One of the problems encountered was the design of a process able to continuously dry granules produced using wet granulation techniques [3].

Wet granulation is a size enlargement technique that turns small particle powder into bigger agglomerates called granules. It utilises liquid binder and is commonly used in the pharmaceutical industry especially for products with particularly high or low percentages of active pharmaceutical

ingredients, or particularly poor flowing materials [4]. A common wet granulation process execution uses a twin screw granulator to produce granules [5], the wet granules need to be dried to remove the moisture and form granules acceptable for further processing.

The dryer has the biggest impact on the residence time of the material along the line taking up to an order of magnitude more time than any other operations. It is also one of the highest energy draw unit operations, as it requires multiple fans and heating elements to operate. For these reasons, it is important to understand the drying behaviour in this particular fluidised bed to be able to optimise the time required for drying, not only to have a smaller residence time but also to optimise the power efficiency of the fluidised bed. The understanding of the behaviour of this fluidised bed could also lead to a simple model that could be used in a control system to obtain dry granules up to specification even when fluctuations are detected.

A few studies on the segmented fluidised bed present in the Consigma-25 line have been published, showing similar drying performances between the different fluidised bed cells and over time during continuous runs [6,7]. An earlier study focused on the use of NIR techniques to detect final moisture content and the effect of different drying condition on the final moisture[8]. Two studies focused on developing mass balances around the segmented dryer in order to better understand and control the drying process in the dryer [9,10], while a more recent study further developed the model in order to predict the final moisture content[11]. Another recent study focused on the granule breakage phenomena during the drying, reporting a noticeable effect mostly due to the pneumatic transport lines utilised [12]. Work on a different twin screw-fluidised bed dryer combination consisting of a ThermoFisher twin screw and a continuous Glatt fluidised bed dryer has also been published; the differences in the dryer design provide insight on different strategies that can be adopted in order to monitor and control the drying process in a continuous line [13–15]. While most of these studies

focus on adjustment of process parameters in the dryer, some work includes the effect of granule size on the drying endpoint [3].

In this study, the temperature profiles of the granules produced at different liquid to solid ratios in each cell are analysed. The liquid to solid ratio (L/S) and therefore the amount of liquid binder was selected as the variable as it is one of the main parameters affecting both the quality of the granules produced in a twin screw granulator [16] and the drying load. The two different control methods available to control the length of the drying in the line are also tested to have a full comparison of the methods available and how they deal with the different L/S. The first method utilises a fixed drying time set as a parameter while the other control method uses a target temperature to define the end of the drying process. An online NIR probe is also employed to measure the residual moisture content in the granule throughout the drying cycle. The average drying rate at different condition is also calculated and used to compare the drying between the different liquid to solid ratios.

2. MATERIALS

Microcrystalline cellulose (Chemicel PH 101, Field Group, Nagpur, India, d50=50μm) and α-lactose monohydrate (Pharmatose 200M, DMV-Fonterra Excipient GmbH and Co., Goch, Germany, d50=55 μm) were used as raw materials. For granulation, a 1:1 blend of MCC and lactose was blended using a helical ribbon blender, and water was used as liquid binder. The initial moisture content of the powder before granulation was recorded to be 2.4%. The blend was processed in a Consigma-25 line varying the L/S ratio in the twin screw granulator in order to observe the drying behaviour in the segmented fluidised bed dryer of granules with different water contents.

3. METHOD

3.1 Experimental

A Consigma-25 (GEA Pharma Systems, Collette™, Wommelgem, Belgium) was used in these experiments. The continuous powder to tablet line Consigma-25 (GEA Pharma Systems, Collette™, Wommelgem, Belgium), used in this study has a twin screw granulator necessitating the utilisation of a dryer.

The twin screw granulator was run at a constant speed of 500 rpm with a constant barrel temperature of 25°C. The L/S was varied from 0.25 to 0.475. Three samples were taken for every condition. In Figure 1a the granule size distribution is shown for the three L/S utilised in the drying experiments where p3 indicates the % for size class based on the volume of the granules. The granules produced at lowest L/S are mostly monomodal while the one produced at higher L/S showed a more prominent second peak at around 1350 µm with the highest L/S having a more pronounced second peak. The amount of fines (<200 µm) (L/S 0.25= 24.2%, L/S 0.35= 26.1% and L/S 0.475= 22.1%) and coarse fractions (1200-1600 µm) (L/S 0.25= 9.0%, L/S 0.35= 13.1% and L/S 0.475= 19.5%) were used to quantify this behaviour showing similar amount of fines between conditions, especially at 0.25 and 0.35 L/S with a more pronounced difference in the percentage of bigger granules. Figure 1b shows the granule size distribution based on the surface area of the granules, this distribution leans strongly towards the fines as smaller particles contribute more towards the total area. Although no assay was conducted in this study, literature shows [17] that bigger granules tend to contain a higher percentage of binder. This inhomogeneity coupled with the fact that the majority of the surface area available for drying is present in the smaller size classes can lead to uneven drying of the material in the granules which can affect the drying behaviour. Although this is important to fully understand the drying behaviour of the different granules in the dryer was not part of the study, which focuses on the average moisture content after drying. The granule size distribution was obtained using a Camsizer (Retsch Technology GmbH, Haan, Germany).

Using a μCT 35 (Scanco Medical AG, Switzerland) X-ray scans of dried granules produced at different L/S ratio are shown in Figure 2. The granules chosen were part of the coarse fraction, and therefore might not represent the porosity present at smaller size classes. Granules from the coarse fraction were chosen due to the higher percentage of moisture usually present in this fraction leading it to have a greater effect on the overall drying. At a close inspection, the granules produced at the low and mid L/S were similar while those produced at higher L/S appered more compacted. The overall porosity of the granules, calculated using the x ray images, were 60% at L/S 0.25, 57% at L/S 0.35, and 51% at L/S 0.475, this porosity includes the large void present in some granules[18]. Local porosities for the granules were also determined by calculating the porosities for smaller areas of the granules which didn't contain large voids, the local porosities obtained were 56% at L/S 0.25, 55% at L/S 0.35, and 44% at L/S 0.475. These numbers confirm the initial visual inspection of the x-ray images. As X-ray scans do not provide a direct measurement of porosity this was calculated via image analysis using ImageJ [19] using the following methodology . An empty part of the scan was used to obtain a treshold black value for empty space, the ratio of the pixels with values under the treshold over the total pixel of the granule area was then considered to be the porosity.

The segmented fluidised bed dryer is divided in 6 cells as shown in Figure 3, each segment is referred to as a cell. Wet granules from the granulator are directed to a cell via a valve positioned at the top of the fluidised bed and the cell is then filled for a finite filling time. When the filling time for one cell has been reached the valve turns and the next cell is loaded. After the granules have been in a cell for a specified drying time (which includes the filling time) or when they reach a target temperature the cell is unloaded via a rotary valve at the bottom of the fluidised bed dryer connected to a pneumatic conveying system. The process can continue indefinitely as the cells are loaded and unloaded sequentially. Each cell of the fluidised bed dryer is equipped with a temperature probe situated just above the air distribution plate in the centre of each cell. Given its location the probe will measure a combination of the air and product temperature depending on its coverage.

Granulation and drying condition were kept constant as shown in Table 1 while the liquid to solid ratio was varied. The variation of L/S at a constant powder feed rate means only the amount of liquid binder, in this case water, was altered during the experiment. To analyse the drying behaviour of the granules the temperature readings of each cell were taken. The temperatures were automatically recorded every 2 seconds. The L/S used were 0.25, 0.35 and 0.475. For each L/S the line was run continuously for 6 cells. To ensure steady state operation one cell before and one cell after were also run but not considered in the data analysis. For the experiments utilising the set temperature to discharge, the cell target temperature was set to 47°C, while for the experiment using constant drying time the time was set to a constant 840s. The final moisture content for each cell was automatically measured by Near Infra-Red (NIR) moisture content probe (FP710e, NDC Technology, Dayton, Ohio, USA) located after the discharge of the granules and before the milling process at the end of the drying. The probe was calibrated using LOD measurement (M35, Sartorius GA, Germany). Eight samples with moisture content varying from 0 to 35% were used to produce the calibration curve. The LOD measurement used 3g of sample and was run at 100°C with automatic end point detection. Each measurement was repeated 5 times. The probe integration rate was set at its standard value of 1s and data was collected every 2 seconds.

For the experiments involving the continuous online measurement of moisture content the NIR probe was fitted to the measurement port located at cell number 5. All experiments were run starting the granulator at cell 4 to avoid any noise from the start-up process. The drying times were altered based on the L/S in order to capture the full drying curve. The twin screw was paused after the filling of cell 6 was complete in order to minimise material requirement. Although this is different from usual continuous operation, it was deemed acceptable as a similar single cell approach showed good correlation with continuous runs in literature [20]. As the experiments were repeated back to back it is important to note that the temperature of the cells in the dryer, when empty, remained stable over the course of the experiment.

4. RESULTS AND DISCUSSION

4.1 Drying behaviour

The mass of dry material in each cell was kept constant at 0.5 kg for all the experiments while the mass of water present in each cell varied based on the selected liquid to solid ratio (Wet mass L/S 0.25: 625g, L/S 0.35: 675g, L/S 0.475: 732.5g). Figure 4 shows that when the temperature behaviour is plotted for the three conditions, the temperature behaves similarly throughout the range of conditions. Although only the temperature of one cell per condition is shown, the behaviour was consistent between the 6 cells. In all cases a sharp decrease in temperature is detected when the cell starts filling with granules, with the decrease in temperature being slightly less steep when less liquid is present. After the cell is loaded with granules, the temperature remains constant for a period of time. The length of this period is related to the L/S, with higher L/S ratio corresponding to a longer temperature plateau. This represents the constant rate drying period. The temperature remains relatively constant near the wet bulb equilibrium temperature until all surface moisture is evaporated. This process takes longer for the higher L/S runs as there is more water to evaporate. After most of the surface water is evaporated the temperature starts to rise. For experiments using a temperature end point for drying, the cell discharge was triggered when the temperature reached 47°C.

The small downward spike found at the end of the drying process is due to the activation of the filter cleaning system which pushes air through the filter to clean it. The final moisture content for each cell when using the constant drying time of 840s was measured giving readings between 1.4% to 3% with the probe located before the milling process. This wide range indicates that this method is not capable of producing consistent final moisture content when such a change in L/S is present and so it would have to be optimised for each L/S, especially if the target moisture is different to equilibrium.

4.2 NIR online measurements

In order to further characterise the drying behaviour in the segmented fluidised bed dryer, online moisture content measurements were taken with an FP710e moisture content probe fitted in the probe port located at cell 5 of the fluidised bed. This probe measures both the moisture content of solids and the amount of material around the probe utilising the total amount of light reflected, which is referred to as product presence. The moisture content reading against the temperature is shown in Figure 4. The experiments were performed at different L/S to assess the impact on the moisture content reading and the drying behaviour. In this case the drying time were varied in order to fully obtain the drying curve of the granules.

The filling time is characteristic for this type of dryer and differs from typical batch dryers as granules are simultaneously loaded in the cells while also drying. Due to this behaviour during the filling time, the overall moisture content increases as the rate of addition of moisture outweighs the drying rate.

At the beginning of the cell filling the moisture content is observed to spike and drop before rising again. This was due to initial material entering the fluidised bed getting detected by the probe but then fluidised away making the probe incapable of providing a consistent reading. This was confirmed by the product presence reading available with the FP710e, which gives an indication of the amount of material near the probe capable of reflecting the NIR light. Figure 4 and Figure 5 show respectively that the moisture content reading and the product presence value drop at the same time confirming the previous hypothesis. This also highlights the fact that during the filling time, the conditions of the granule bed are constantly evolving and therefore extra care should be taken to avoid excessive elutriation or potential blockage of the distributing plate caused by overwetted granules as this can impact the final product qualities or lead to equipment malfunction.

After the filling time was completed (highlighted with a vertical solid line), the moisture content decreased as expected at a fairly constant rate until the critical moisture content was reached, where

the drying rate drastically reduced. In this case the moisture content never dipped below 1.4% and remained constant at the end of the drying indicating being close to equilibrium.

The product presence also decreased over time after the filling was completed with a larger impact shown in the lower L/S; this is likely due to the larger proportions of fines present at the lower L/S, which get pushed towards the top of the bed and away from the probe. In addition to this, over the course of the drying process, granule density decreases as water is evaporated which causes more granules to float higher towards the filter, away from the probe range. This behaviour was confirmed via observation of the fluidising behaviour during the drying process through the glass window on the side of the cell. In Figure 6, where the pressure drop over the top filters is shown, it is possible to see how the pressure drop increases over the drying time while the product presence decreases due to the build-up of material on the filters.

An experiment was also performed, where the fluidised bed cell was filled for 360 s instead of 180 s at a L/S of 0.35 in order to achieve a higher amount of material in the cell and ensuring probe coverage throughout the drying process. The result of this is shown in Figure 7. This shows how the product presence graphs were nearly identical in the first 180 seconds as expected but the product presence then stabilised when more material was added, remaining constant throughout the drying time. This again highlight the importance of the filling process in producing a stable bed and should be investigated in further research.

The spikes present at the end of the drying in Figure 5 and Figure 6 are caused by the activation of the filter cleaning system (blowback) which pushes air through the filter while the cell is emptying. This ensures that the all the material that was in the cell leaves. The use of blowback also keeps the filters clean for longer periods which is shown by the reduced drop in pressure over the filters after its activation. The spike of material and the reduction in product presence which can be observed during the drying process is due to the elutriation of the fines from the granules. Although this was

not the focus of the study, this behaviour might affect the drying and should be taken in consideration especially in the context of manufacturing where it could lead to problems in material tracking. Also, the pressure drop over the filters of the dryers can be used to monitor the extent of material remaining on the filter. Overall, the product presence reading tends to be particularly noisy because of the turbulent environment present near the probe.

The drying time was considered to be completed when the residual moisture content detected was below 2% as this would be lower than the residual moisture content recorded for the blend before granulation, which was recorded by positioning the probe in the material before granulation.

4.3 Optimal drying time estimation

One of the objectives of the study was to optimise the drying efficiency of the process. The use of the derivative of the cell temperature over time was investigated as an indicator of drying efficiency. Figure 8 shows the derivative over the drying cycle; the first negative variation is caused by the beginning of the filling process which causes a steep drop in the cell temperature which then stabilises. After around 400s the temperature starts to increase as the surface moisture is mostly evaporated and the drying transitions to the falling drying rate period. The derivative peaks at around 580s, after that the change in temperature slows down as it approaches the drying air inlet temperature. The time between the two peaks was considered an optimal drying time in this study. NIR moisture data was collected for 6 drying runs at each L/S at the peak derivative time (Table 2). The overall moisture content average obtained via this method was 2.4±0.2%. At longer times than detected the drying is less efficient as shown in Figure 4, although more time is required to reach the 2.0% moisture target. To improve the method further, a study focusing on the correlation of the derivative peak and the process variables, e.g. dryer inlet temperature is needed.

The optimal drying times for each cell were averaged and plotted against the L/S (Figure 9). The data shown in Table 2 suggest that the differences in the reported temperatures in the different cells

have little effect on the method performance. This suggest the derivative method is a robust approach for control and optimization of dryer. In addition, the linear trend found between L/S and drying time can be used to predict optimal drying time as a function of L/S when the other parameters are kept constant.

4.4 Average drying rate

To be able to calculate the optimal drying time for different conditions such as higher throughput or higher filling time of the cells which might be required by the process and to assess if the differences in L/S affected the drying, an average drying factor was utilised. This was calculated from the mass of water evaporated and the optimal time. The mass of evaporated water was obtained by subtracting the residual mass of water in the granules, derived from the moisture content reading, from the mass of water added to the process during granulation. The amount of water evaporated was then divided utilising the time obtained via the derivative method. As shown in Table 2, the rate of drying remained the same at L/S of 0.25 and 0.35 and was slightly lower at 0.475. Further studies focusing on the effect of the particle size and the liquid distribution across the granule size is required to fully understand the effect of the larger granules and lower porosity [21] at the higher L/S.

4.5 Target temperature discharge

In this set of experiments, the fluidised bed was set to unload a cell when it reached a specific temperature. The temperature selected was 47°C. This temperature was selected based on the previous experiments where the profile plateaued above this based on the 60°C air temperature used in the study. This temperature is strongly related to the drying conditions, especially the drying temperature, and therefore the collection of new drying curves would be required if the conditions were varied.

The moisture content readings obtained when utilising this method were consistent (L/S 0.25= 1.9±0.1%, L/S 0.35= 1.9±0.2% and L/S 0.475= 1.8±0.1% and an average overall of 1.9±0.1%, with

± indicating the 95% confidence interval) indicating that this method can be successfully employed to dry granules produced with varying amount of liquid to obtain a target moisture content without the need for trial and error when drying conditions, especially temperature, are kept the same.

The previously discussed derivative method to detect the optimal drying time and the time to reach 2% residual moisture in the NIR experiment are also shown in Figure 9. The lines are nearly parallel with the difference in offset caused by the different final moisture content that the different methods target with longer times leading to lower moisture contents. Both the NIR and derivative method drying time showed an average variability of less than 2.5% across the different L/S tested while the temperature method showed a higher average variability at 8.2%. This is most likely because each cell temperature reading at steady state was slightly different and needs to be considered if the residence time across the line requires consistency. The bigger time variability did not translate to a higher final moisture content variability. The lower final moisture content achieved by the temperature method might contribute to smaller variability in the measurement as it is closer to the equilibrium moisture content.

The difference in final moisture content value between methods shows that although the derivative method can be used to detect an efficent end of drying it does not detect the point of equilibrium as further drying can be achieved.

4.7 Methods comparison

The two methods to select the discharge time in the fluidised bed of the Consigma-25 line have both advantages and disadvantages. Setting a constant drying time ensures that the process performs at a constant residence time. It is also a robust system which does not rely on any sensor that could deviate during the process. The lack of sensor utilisation is also the main downfall of this method as it is not able to react to disturbances such as environmental changes or upstream deviation from the

set point, requiring the drying time to be optimised every time a parameter that influences the drying is changed.

Conversely, operating the dryer using the end temperature setting, managed to obtain consistent drying of the granules at different L/S, making it a versatile option capable of responding to fluctuations. This stability might also be partly due to the temperature that was selected driving the granules very close to the equilibrium point, so careful attention should be taken to consistency if aiming for a higher moisture content at a lower target temperature, especially if the temperature recorded differs between cells. In the case of a change in the drying air temperature the ideal target temperature for the process will have to be located again via trial and error or via recording a new drying curve using NIR moisture reading, this also applies to the derivative method as it will point at a different moisture content.

The method using the derivative of the temperature and detecting the minima and maxima devised in this paper is an attempt to create a method which reduces trial and error to obtain the optimal drying time. This approach can be used to identify when the drying rate drops considerably and was able to target a consistent moisture content. If a different moisture content was required for the final product, the method could be used to identify the optimal inlet air temperature where the derivative would peak at the moisture content required. The applicability of the method at different working conditions and with different materials is outside the scope of the study but will be part of future investigations to further refine and test the application limits of the method. As the derivative can be calculated in real time a control system sensing the second peak could be also put in place to detect the end of the drying and initiate the unloading of the cell automatically.

Continuously recording the moisture content of the granules with a NIR probe was also confirmed to be possible, giving a direct reading of the moisture content in real time. This method also has disadvantages, as shown in Figure 4 and Figure 5 where insufficient material present in the vicinity

of the probe can lead to unrepresentative readings. Other concerns are both location and cost. In the current configuration only cell number 2 and 5 can be equipped with extra probes and these would need additional investment as they are not fitted to the equipment as standard.

5. CONCLUSIONS

The drying behaviour of the granules was observed via the inbuilt temperature sensor and moisture content probe. The drying time appears to correlate linearly with the amount of water present in each cell. The effect of particle size was not a focus of this study and seems to have an effect on the drying rate at the highest L/S and should be investigated further.

The behaviour of the moisture content during the filling time was captured providing further insight in the drying operation of the fluidised bed dryer while it is filled continuously. The characteristic behaviour of the moisture content stabilising during the filling time could provide further information particularly on the efficiency of the drying. For example, a reduced drying capacity due to clogging or bad fluidisation should result in a higher moisture content during the filling phase. Being able to detect this issue quickly presents the possibility of controlling parameters both in the dryer or twin screw granulator to minimise the impact on the final moisture content and also to monitor correct operation of the dryer. The importance of sufficient coverage of the NIR probe was also shown, which is particularly important at the beginning of the filling time.

The alternate end of drying detection method showed similar trends in drying time. The target temperature method produced granules with consistent final moisture content although the method is dependent on determining a suitable selection based on experimental trials. The model devised in this study utilising the derivative of temperature also managed to obtain consistent moisture content values and showed a smaller variability in predicted drying times. This could be due to the difference in the temperature readings from each cell, which has a greater impact on the target temperature

method, which utilised the absolute temperature value, while the derivative method relies on temperature difference. However, this difference did not seem to affect the consistency in the final moisture content of either method. As the derivative method identifies the point where the efficiency of drying diminished drastically it could be further developed to select an optimal inlet air temperature for a specific moisture content.

The simplicity of the derivative method allows it to be used in real time making it viable to be implemented in an online control system after further testing its robustness over more drying conditions. Although other more complex soft sensing techniques can be considered, there is a real challenge for these to be adopted in industry. The derivative method simplicity and relative ease of integration can act as a stepping stone towards more advanced control strategies during production in the pharmaceutical industry.

As the interplay of different units and their parameters on critical attributes is critical in this kind of equipment, flowsheet models comprising of the different unit operation would be a powerful modelling tool in the future. These could not only be used to reduce the amount of experimental work required but also run alongside the equipment as a soft sensor for a variety of properties such as moisture content during the drying process in each cell. These sensors could then be implemented in control strategies to further improve performance and to make the control systems more reliable.

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