BFS BOHLE FLUID BED SYSTEMS, MULTIPURPOSE EQUIPMENT FOR DRYING, GRANULATION AND COATING

Introduction

Fluid bed equipment has been well known and established in the pharmaceutical industry for more than 50 years [1]. Originally used only as a dryer after a wet granulation process, it replaced step wisely the classical oven drying in pharmaceutical production.

Today, fluid bed drying can still be considered state of the art within pharmaceutical drying processes. With the additional implementation of spray nozzles fluid bed dryers became fluid bed granulators - thus wet granulation could be smoothly performed in one discrete device.

In these applications the nozzles were mounted on the top in order to spray onto the wet particles (top spray setup). Further development used the same apparatus for coating of tablets or other particles with an additional insert [2] whereby the spray nozzles were placed at the bottom of the fluid bed (bottom spray setup). This type has been used for decades in the pharmaceutical industry.

Other innovations later developed, for example rotor or spouted fluid bed devices. However these types can only be found in niche applications. The most promising change was the development of the fluid bed apparatus with tangentially mounted nozzles. This method is now considered state of the art equipment for several reasons:

Compared to the classic top spray design, tangential fluid beds offer drying, granulation and coating in one device without any setup change or additional inserts. As the wet particles, granules or small tablets move in a tangential manner with quite a low level of fluid, a high expansion volume is not needed as before with the classic top spray equipment. This scenario significantly reduces the installation height of fluid bed equipment and needs less production space, thereby presenting cost saving opportunities.

With this in mind L.B. Bohle developed the Bohle Fluid Bed Systems with tangentially mounted spray nozzles and the Bohle Uni Cone BUC® [3]. The equipment is available for batch sizes ranging from 1 to 500kg. Built in 12 bar shock resistant execution, organic and water based processes are always accessible.

Short product transfer times and an effective cleaning offer opportunities for additional savings in production time and costs. By design all machines are geometrically similar which enables an easy scale up procedure.

In Figure 1 a typical production scale fluid bed apparatus is displayed with corresponding HMI. The Bohle Uni Cone BUC® (Figure 2) is a specially slotted air distributor plate with a conical displacement cone. These features create a complete particle fluidization which guarantees high coating uniformity without particle twinning issues. Besides experimental testing, this tangential particle movement was analyzed and proved by means of a combination of computational fluid dynamics (CFD) and discrete element methods (DEM) [4].

The aim of the following case studies is to show and to prove the versatility of the Bohle Fluid Bed System for granulation and coating applications.

Figure 1: Bohle Fluid Bed BFS 240 with HMI

Figure 2: Bohle Uni Cone BUC® with tangentially mounted spray nozzles within a BFS 30

Case study I

For a classical wet granulation experiment a placebo formulation was chosen containing fine lactose and corn starch as filler and povidone as wet binder (Table 1). To achieve a more homogeneous binder distribution within the final granules povidone was added as a binder solution [5].

The experiment was performed with a BFS 30 (Figure 2), a pilot scale fluid bed system containing 2 spraying nozzles and typically suitable for batch sizes ranging from 5 to 40kg (dependent on bulk density).

Table 1 Placebo granule formulation (batch size: 15 kg) Methods

Formulation	
Granulac® 200	85
Corn starch	15 %
Kollidon® 25	5 %
Granulation liquid	water

Table 2 Settings for wet granulation of the lactose formulation in a BFS 30

Parameters	
Spray rate	170 g/min
Atomization pressure	0.7 bar
Inlet air volume	450 m³/h
Inlet air temperature	70 °C
Product temperature	26 °C

After a warm up phase which also serves for homogeneous blending of the placebo mixture, the granulation phase was performed at a spray rate of 170 g/min and an atomization pressure of 0.7 bar. Amount of inlet air volume was set by visual judgment. Drying was done subsequently at the same settings for inlet air volume and temperature.

After granulation the final granules were passed through a conical sieve (Bohle Turbo Sieve, BTS 200) using a 1 mm rasp sieve.

Finally, sieve analysis results reflected a proper agglomeration of the original powder with quite a narrow particle size distribution with a small amount of fines (Figure 3). The lactose granules also showed a spherical shape which is typical for tangential fluid bed agglomerates (Figures 4 and 5). The shape also led to a very good Hausner Factor of 1.1 and a bulk density of 0.54 g/mL.

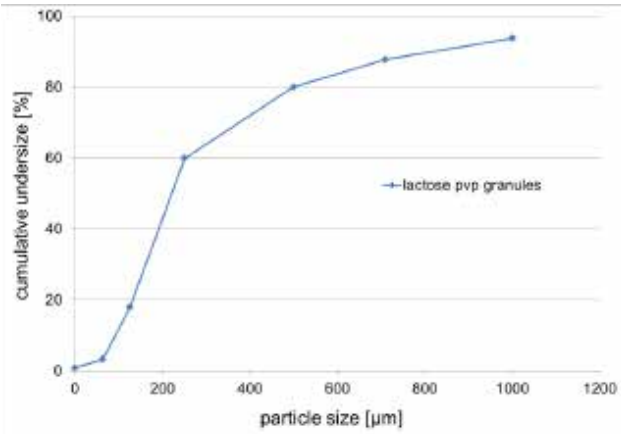

Figure 3: Particle size distribution of placebo granules

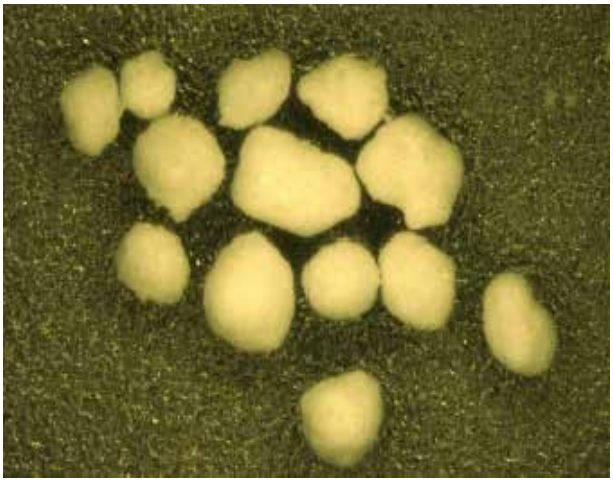

Figure 4: Lactose granules (light microscope, magnification: 50x)

Figure 5: Single spherical lactose agglomerate (light microscope, magnification: 50x)

Case study II - Pellet Coating

The goal of the first pellet coating study was to produce a sustained release multiparticulate capsule formulation using a BFS 30 in the context of a reformulation of commercial product. For this already existing product a classical fluid bed with Wurster insert was used for production and pellet curing was performed in a traditional oven.

The basis for the reformulation process was 15kg of Cellets® (d=500µm) which coated in a first step with an active layer and additionally in a second coating step with a sustained release polymer dispersion. The first coating solution contained a high amount of dissolved API and povidone as wet binder (Table 3). The viscous solution was applied using parameters shown in Table 4.

Table 3 API coating solution (133 % mass gain)

Formulation	
API	22.5 %
Kollidon® 30	7.5 %
Water	70.0 %

Table 4 Settings for the active layering in a BFS 30 (spray phase)

Formulation	
Spray rate	100 g/min
Atomization pressure	2.5 bar
Inlet air volume	900 m³/h
Inlet air temperature	55 °C
Product temperature	39 °C

After the coating phase a short drying phase was introduced at same inlet air conditions for several minutes. The spray guns had to be cleaned properly before the sustained release polymer dispersion (Table 5) could be started. Settings for the spray phase are displayed in Table 6.

Table 5 Sustained release coating dispersion

Formulation	
Eudragit® NE 30D	50.8 %
Tween® 80	0.8 %
Syloid® 244	4.6 %
Water	43.8 %

Table 6 Settings for the sustained release coating (10% mass gain)

Parameters	
Spray rate	75 g/min
Atomization pressure	1.5 bar
Inlet air volume	950 m³/h
Inlet air temperature	32 °C
Product temperature	23 °C

Curing also took place with the same equipment at 950m³/h inlet air volume at 50°C for 3 hours. Previous experiments in which oven curing was compared to curing within the fluid bed had shown that 24 hours were needed to achieve the same curing results in a traditional oven. Thus using the same equipment not only made the whole process much simpler but also significantly shorter compared to the traditional approach to processing.

Finally, drug dissolution was tested in demineralized water which proved the successful sustained release coating (Figure 6) and a successful reformulation.

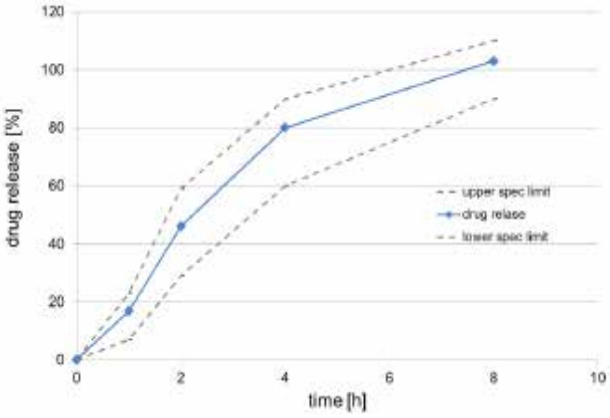

Figure 6: Drug dissolution in demineralized water after fluid bed curing for 3h at 50°C

Case study III - Pellet coating

The third case study deals with a sustained release pellet formulation which was processed in production scale Bohle Fluid Bed Systems (BFS 120 and BFS 240).

First, Cellets® (d=250 µm) were coated with API and a typical wet binder until 25 % mass gain. The second coating layer consists of a sustained release polymer solution containing ethyl cellulose until 120% mass gain.

During coating of the second layer the initial batch had to be divided up into three sub batches due to strong increase in bulk volume and mass gain. Final pellet size was about 700 µm. Coating in a BFS always led to high yields (≤ 0.4 % agglomerates) even after processing for 7 days in a three shift operation.

Figure 7 shows sectional views of the final pellets: the coherent coating layer could be seen as well as the initial API layer.

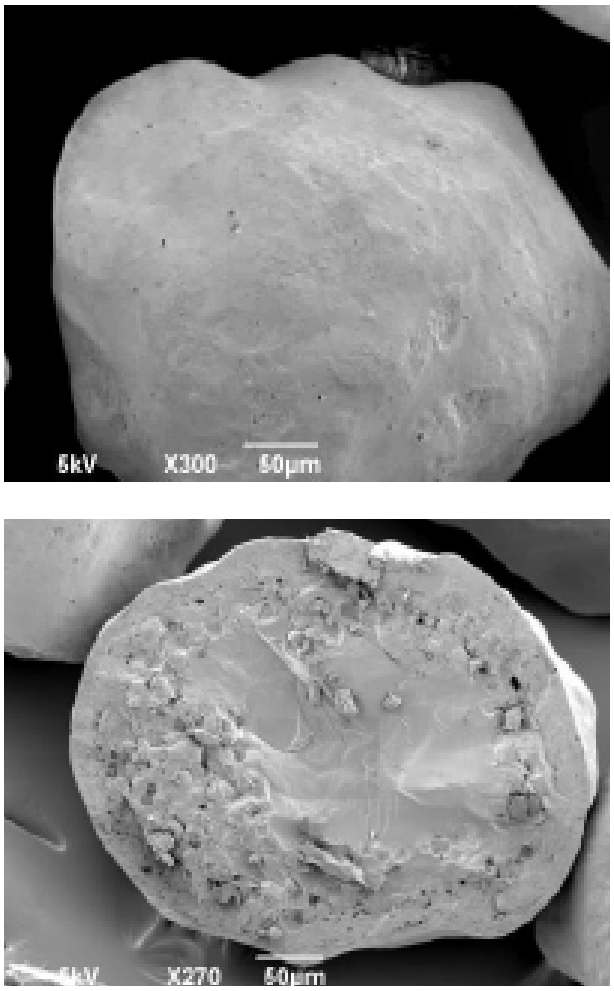

Figure 7: SEM photos of sustained release pellets (sectional view)

Conclusion

Using tangential fluid bed technology represents state of the art in pharmaceutical manufacturing for particle coating, granulation and drying. Furthermore with the innovative Bohle Uni Cone BUC® a complete particle fluidization is assured which leads to high coating uniformities and high yields in the final product due to absence of particle twinning effects.

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