

1|2014

INNOVATIV



BOHLE



Dear reader,

One of the two leading trade fairs in Germany, the Interpack 2014, invites you from May 8th –14th for a visit! We have spared no effort to show you our newest revolutionary development in the field of pharmaceutical granulation at the Interpack.

Our BUC® process, the Bohle Uni Cone, has opened a new page in the

book of granulation technology. We have designed the technology so that there are advantages to both the pharmaceutical side and the handling side during the Bohle Uni Cone BUC® process. With this new process, wet granulation, drying and pellet coating are possible, without modification and in one bowl! This combination is not possible in the 55 year old Wurster process without the alteration of the machine.

The individual process times can be observed very well through the windows. In addition, variations of the individual variables can be checked visually and are controllable. A visual inspection is not possible in the Wurster process and the quality of the batch can be only seen at the end of the process. In addition, due to the conical fluid bottom, we set a further important development. The pellets are not only encouraged tangentially because of the tangential air flow, but because

the conical fluid base, they also move in a radial direction as well. Because of this second component, it is no longer necessary to install inner nozzles at the bottom. Through the tangentially mounted nozzles, a uniquely high uniformity can be reached across the batch.

Last but not least, next to the technical highlights at our Interpack booth D 27 in Hall 3, we will have a raffle of special charm. If you want to start dynamically in the summer of 2014, you should visit our booth.

Good luck for your visit

The new Plant 3 in Ennigerloh



L.B. Bohle invests in processes, research and production

L. B. Bohle Maschinen + Verfahren GmbH sets three important milestones for the future at the Interpack 2014 trade fair. The Bohle Uni Cone BUC® process will be presented in Düsseldorf for the first time. The newly built Technology Center at the Ennigerloh headquarters will be opened in the middle of the year. In the new Plant 3, the process machine production has started. "With investments into the future, we ended a very successful 2013 financial year", Lorenz Bohle, CEO of the L. B. Bohle Maschinen + Verfahren GmbH, summed up.



The construction in the Technology Center is progressing according to plan. The building will be opened in early autumn.

With the Bohle Uni Cone BUC® process which even coats small particles much more precisely and evenly Bohle offers the alternative to the conventional Wurster process. "We have developed two major modifications that solve the problem of the Wurster process", says Bohle. A sloping floor and a conical tip in the center provide a homogenous swirl of the product. Simultaneously, the coating substance is sprayed through tangential nozzles. We thus achieve an unrivalled coating uniformity. With this process, customers can also apply active substances on their products with highest precision.

Lean Production creates the competitive edge

Also in their own production, L.B. Bohle counts on optimised processes: The relocation to the new Plant 3 has been completed and Lean Production is gradually being introduced. "We closely involve our suppliers in this process", said Bohle. The production in the new plant will be standardized and more efficient. Machines can thus be delivered in four to five months instead of seven months.

Knowledge transfer in Ennigerloh

For Bohle, knowledge transfer to

the benefit of the customers is also decisive for investments in the Technology Center which is currently under construction in Ennigerloh. Our customers are increasingly relying on continuous production processes. "In the Technology Center, we will visualize the entire production line in one plant and develop and present optimized processes in cooperation with the Universities of Düsseldorf and Graz as well as the measurement, control and process experts from Siemens", Lorenz Bohle outlined the goals. Two million euros will be invested in the glass-fronted building alone.

Global growth opportunities

In the 2013 financial year, L. B. Bohle Maschinen + Verfahren GmbH generated sales of around 42 million euros. The investments lay the foundation for further sales growth. "Now, we have to give our customers a stronger sense of the variety of our product portfolio which ranges from simple handling machines to complex solutions – including software" explains Bohle. On the world market, he currently sees great growth opportunities in Russia and South America. "In South America, we will intensify our activities through a new sales expert", says Bohle. In Russia, too, a positive development for 2014 can be expected "with several major orders". The most important market will remain the USA with about 30 percent sales. The excellent features of the blending

and coating machines will be promoted in a sales offensive for further market penetration. However, the managing director takes a rather critical view on the situation in China and the emerging

pharmaceutical market in India. The general market conditions and the legal protection of own technologies urge Bohle to be cautious.



The process machine production is already running smoothly in Plant 3. The optimisation of working processes ensures short delivery times.

Interphex 2014

Exhibition a big succes

The annual international pharmaceutical equipment trade show "Interphex" took place in New York on March 18–20. As a highlight Bohle presented the BRC 100, dry granulator. It attracted the attention by the attendees and was praised for its innovative design and many process advantages. The BRC 100 will be installed in the U.S. Service Center in Warminster, Pennsylvania, and is available for being tested by the customers. Already, multiple trials have been booked for the latest addition to the Bohle product line over the next few months.

In addition to displaying the Roller Compactor, Martin Hack – Vice President and General Manager of L.B. Bohle LLC – gave a lecture on innovations in continuous solids production with a highlight on the Bohle semi-



Martin Hack (left), Vice-President of the Bohle LLC, in front of the BRC 100, that enthusiast the mass

continuous coater, the KOCO® 50. The lecture was full to capacity with a thorough discussion of the direction continuous processing is taking the pharmaceutical industry. There is a lot of anticipation for L.B. Bohle to complete the new Technology Center

at its headquarter in Ennigerloh, Germany, which will house a complete continuous solid dosage production line for testing and evaluation by our customers.

Interpack Düsseldorf

A world novelty at the trade fair

At this year's Interpack, which will be held from 8 to 14 May in Düsseldorf, the Ennigerloh-based machine builder L.B. Bohle will be present.

In addition to the well-known product portfolio – comprising coating machines and granulation solutions – L.B. Bohle will present a product innovation at the Interpack:

the Bohle dry granulator BRC 25. The smaller version of the BRC 100 compactor which celebrated its world premiere at theACHEMA 2012, extends and optimizes the product portfolio of the machine builder from Ennigerloh in the granulation segment. Thus, Bohle provides the largest offer of granulation options of all manufacturers and continues to extend its portfolio.

With the Bohle Uni Cone BUC® process, Bohle presents the latest stage in development of this technology, which was introduced in 2013 to the trade professionals. "With the BUC process, we can coat even the smallest particles more precisely and evenly", explains Lorenz Bohle with regard to the most significant added value. Moreover, Bohle will be presenting its granulation system Compact Unit in which individual components High Shear Granulator GMA, Bohle Fluid Bed System BFS, Wet Sieve and Dry Sieve BTS as well as a cyclone separator are optimally integrated into one unit.

Bohle will also present its technological edge in the film coating technology.



You will find us in
Hall 3 – Booth D 27

We look forward to welcoming you!



The booth at the Interpack trade fair which was again designed by the Hamburg-based MAV, stands out with its clear structure and elegance.

BFS Bohle Fluid Bed Systems

Multipurpose equipment for drying, granulation and coating



Figure 1: Bohle Fluid Bed BFS 240 with HMI

Introduction

Fluid bed equipment is well known and established in the pharmaceutical industry for more than 50 years now [1]. Originally used only as a dryer after a wet granulation process, it replaced stepwise the classical oven drying in pharmaceutical production. Nowadays, fluid bed drying can be considered still as state of the art within pharmaceutical drying processes. With the additional implementation of spraying nozzles fluid bed dryers became fluid bed granulators – thus wet granulation could be elegantly performed in one discrete device. In these applications the nozzles were mounted on the top in order to spray onto the fluidized particles (top spray setup).

A further development was to use the same apparatus for coating of tablets

or other particles with an additional insert [2] whereas the spray nozzles were placed at the bottom of the fluid bed (bottom spray setup). These equipment types are being used since decades in pharmaceutical industry. Other innovations came up later, as 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 form is considered nowadays as state of the art equipment due to several technical reasons: Compared to classical top spray setups, tangential fluid bed equipment offers the possibility for drying, granulation and coating in one device without any setup change or additional inserts.

As the fluidized particles, granules or small tablets move in a tangential manner with a quite low fluidization height; a high expansion volume is not needed as known from the classical top spray equipment. This circumstance significantly reduces the installation height of fluid bed equipment and needs less production space which also offers the opportunity to save costs.

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. As it is always built in 12 bar shock resistant execution, organic and water based processes are 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 are responsible for a complete particle fluidization which is a guaranty for a high coating uniformity without particle twinning issues. Besides experimental experiences 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.

Case study I Wet granulation

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 usually capable for batch sizes ranging from 5 to 40kg (dependent on bulk density).

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

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



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

phase was performed at a spray rate of 170g/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 1mm rasping sieve.

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

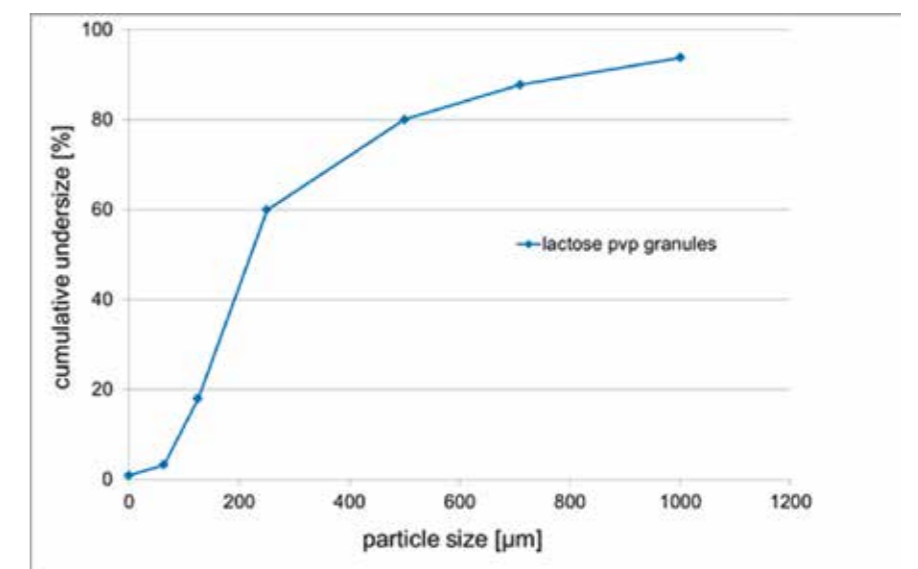


Figure 3: Particle size distribution of placebo granules

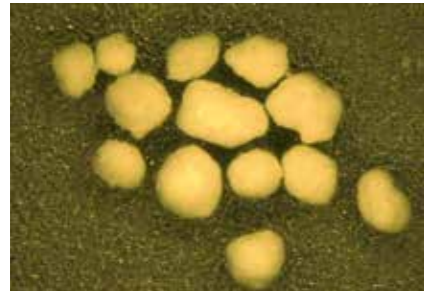


Figure 4: Lactose granules (light microscope, magnification: 50x)



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

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)

Parameters	
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 was as well performed within 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

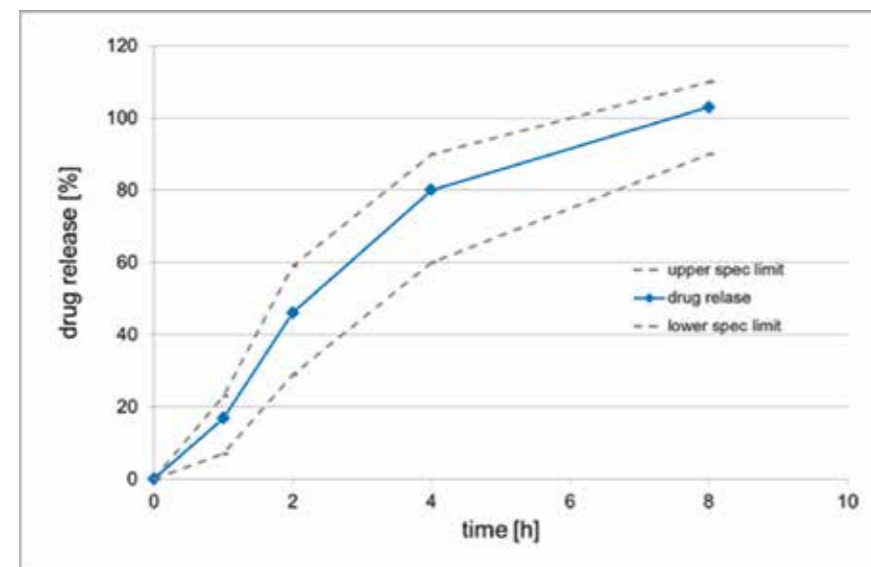


Figure 6: Drug dissolution in demineralized water after fluid bed curing for 3h at 50°C

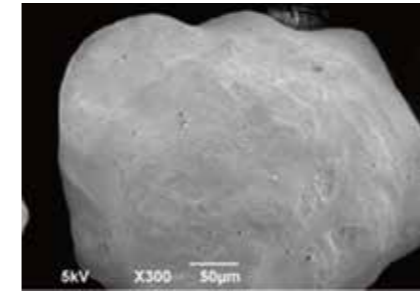


Figure 7: SEM photos of sustained release pellets (sectional view)

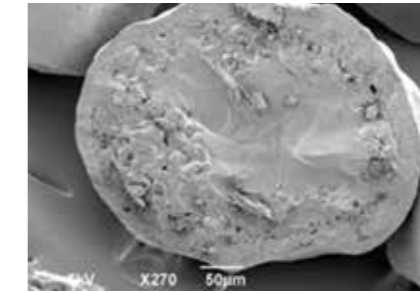


Figure 8: SEM photos of sustained release pellets (sectional view)

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 a traditional approach of processing.

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

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). In a first step Cellets® (d=250µm) 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 700µm. Coating in a BFS led always to high yields (≤0.4% agglomerates) even after processing for seven days in a three shift operation. Figure 7 shows

sectional views of the final pellets: the coherent coating layer could be properly observed as well as the initial API layer.

Conclusion

Using tangential fluid bed apparatus 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.

- [1] Parikh D.M., Bonck J.A., Mogavero A. Batch fluid bed granulation, Handbook of Pharmaceutical Granulation Technology, Marcel Dekker, New York 2007.
- [2] Wurster D.E. Particle coating apparatus, patent application 1964, US 3241520 A22
- [3] Bohle Uni Cone BUC®, eingetragenes Handelszeichen 2012, Nr. 01659067
- [4] <http://www.lbbohle.de/en/process-machines/granulation/bohle-fluid-bed-system-bfs>
- [5] Serno P., Kleinebudde P, Knop K. Granulieren, apv- basics, Editio Cantor Verlag 2007

Dr. Dejan Djuric,
Manager Scientific Operations



Bohle Coater available as Lego® model

Creativity unchained at Bohle

It is actually by coincidence that Bohle employee Michael Jasper had the idea to replicate a Bohle Film Coater BFC 600. When cleaning up and sorting his numerous Lego® bricks, he suddenly held a brick in his hand which looked very similar to the front door of the BFC.

Thus the idea of a miniature version of the coater was born and so the engineer Jasper planned and developed the model. At first, he created a digital model on the computer for estimating the number and type of bricks needed. After several weeks of planning and construction, he finished the prototype of the Bohle Film Coater BFC 600. His colleagues were immediately excited about his know-how and attention for detail.

It was therefore just a matter of time before the first customer showed in-

terest in the "mini BFC" during his visit at Bohle where he actually wanted to discuss an original BFC 600 project. He then ordered four Lego® models of the BFC 600. At the end

of November, the models of the high tech coater at the scale of 1:24 were finished and shipped to the customer shortly after the delivery of the original BFC 600.



Accuracy in perfection – Michael Jasper next to one of his Lego film coater.

Employees awarded for improvement suggestions

Award ceremony at Christmas party



At the Christmas party, improvement suggestions were awarded. The picture shows from left to right Lorenz B. Bohle, Oliver Wagemann, Peter Pelz, Christiane Fischer, Andreas Niemerg and Katharina Brandenburg.

At the L.B. Bohle Christmas party in 2013, five employees were awarded for their ideas regarding the optimization of company processes.

The improvements both related to mere organizational processes and to technical production processes. Company founder Lorenz B. Bohle expressed his sincere thanks to the five employees and welcomed the innovative spirit.

Lorenz Bohle portrayed in the documentary "Going Global"

Premiere took place in Münster in October

In early 2013, director Harald Redmer asked Bohle whether it was possible to portray Lorenz B. Bohle in a film. "Going Global" portrays five entrepreneurs from the Münsterland region whose companies are driving forces and market leaders in various industrial branches.

Contrary to the widespread assumption that the Münsterland region is

mainly characterized by agriculture and local recreation, it has a lot to offer in terms of industry. Thus, Redmer created an individual and most of all pleasant portrayal of all five companies.

Lorenz Bohle gave an account of the challenges and difficulties in the early development stages of the company. Then, he outlined the success story

of his company and its expansion to being the technology and market leader in mechanical engineering for the pharmaceutical industry.

Learn more at:

Unfortunately, the documentary is available in German only.



Four art exhibitions attracted many visitors in 2013

Multifaceted paintings and sculptures

Visitors were offered a broad spectrum of paintings and sculptures at the four art exhibitions which took place at the Bohle Service Center in 2013. The exhibitions, which exclusively showed works from artists of the Kreiskunstverein Beckum-Warendorf, were especially multifaceted.

The artist Barbara Davis opened the exhibition year with her vibrantly coloured works under the motto "The Good Times Revisited". Peer Christian Stuwe filled the second art exhibition of the year with sculptures and huge rippings. In the third exhibition, the artist Birgit Rumpf presented her portraits. The works "Eyewitnesses: Portraits and Eggheads" represent a comparison of two ideas that tell a similar story with

another character when juxtaposed and developed further.

Gordon Brown from Hamm concluded the exhibition year. In addition to wall drawings, the exhibition focused on wooden sculptures.

All four exhibitions recorded a high number of visitors so that the art presentation partly had to be extended. Visitors can look forward to a multifaceted and interesting exhibition year 2014 as well.



Dr. Bennie Priddy, the scientific guide of the Bohle exhibition series, explains the works of Birgit Rumpf

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