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BOHLE INNOVATIV

WE DEVELOP YOUR FUTURE.

EASY FLOW®

Advancement of a revolutionary system

In issues # 2-2007 and # 1-2008 we presented the EASY FLOW® continuous granulation system with downstream dryer. In this issue, we present some advancements of the system designed to increase efficiency and optimize pharmaceutical production.

- The previous single-fluid spray nozzle has been replaced by a two-fluid nozzle with atomization air. This immensely enhances liquid dispersion onto the product bed.
- The dosing unit is now separately mounted, eliminating any interaction with the agitation system. Subsequently, →

In this issue:

Dear readers,

March 2009

In its quest for state of the art and cost effective production methods, the pharmaceutical industry has the opportunity to use Bohle systems for their trials and production.

One of the latest Bohle innovations, the Bohle EASY FLOW® continuous granulation system, offers some amazing new developments:

The direct opposite of conventional batch processing is the continuous production of solid dosage. Wet granulation and drying occur constantly. The wet granulator is a high speed blender featuring the well known and robust Bohle single pot technology. Feeding of solids and fluids is automatic. Process control is similar to other Bohle processing equipment. Furthermore, you have the option to integrate particle size measurement via NIR or laser. Drying takes place in a rotating chamber which is heated from the outside. Through the rolling motion, heat dries the particles. A specialized scraper cleans the wall of the tube and also mixes the granules such that all particles are evenly dried.

During Achema 2009, the EASY FLOW® system will be our featured product. In a high definition product presentation, you will see the new Bohle EASY FLOW® system combined with a Fette tablet press.

We will also present a number of additional Bohle products. An amazing example of the future orientated-fluid-bed technology made by Bohle will be shown. You will be able to examine the product bowl of a Bohle-Fluid-Bed-System BFS with its tangential spray arm and perforated bottom plate. To illustrate the heart of Bohle coating technology, you will see the coating drum of a BFC 400 Bohle-Film-Coater. A laboratory blender equipped with NIR technology will also be presented at the exhibition. Last but not least, we will show the BCK 200 Bohle-Containment-System.

As you can see, a visit to the Bohle team in hall 3 on stand H17-K21 at Achema 2009 will be well worth the time! We hope to see you there!

Yours sincerely,

→ Continuation: EASY FLOW®

dosing of solids is much more accurate.

- The EASY FLOW® impeller is redesigned and upgraded via modified geometry. The blade surfaces have been reshaped so more pressure can be applied to the product. This increases the number of possible applications for the Bohle continuous granulator.
- The geometry of the chopper has also been improved. Due to its integral design, granules are transported directly from the impeller area to the sieve. The revised design helps to avoid product adhesion. Furthermore, this new design permits more precise transportation of product to the sieve. Further improvement is possible by varying the chopper's rotary speed!
- The newly optimized solid dosage vacuum feeding system is amazingly fast and easy to clean and exhibits no product leakage.
- The changeability of the sieve has been updated as well. Now it is possible to customize the sieve to accommodate different products.
- These innovative advancements noted above help to optimize your daily production and will give you even more motivation to change from batch to continuous production! ■

Development of a new sustained release pellet coating process

For this development, Non Pareil pellets needed to be active layered and finally coated with a sustained release film. The original manufacturing process used solvents and was done in a Pellegrini pan. The whole process was very long and difficult to control which lead to a not acceptable batch rejection rate.
Goal was to develop a new aqueous process for a fluid bed granulator and coater which generated the same active release profile as the old process. Considering that solvent based process will be replaced by an aqueous process, excipients and process parameters could be changed.
Development work was done in a Bohle BFS 30 fluid bed. Production scale is to be done in a BFS 240. In total we did two active layering processes to achieve instant release (IR) pellets. Each of the IR coated batches was split into three sub batches for the sustained release coating.

Active layering process

The active and the binder were mixed together in water. The active was partly dissolved, but most remained suspended in the water. The active coating liquid was sprayed with one three component nozzle into the Non Pareil pellets. Bed temperature was adjusted to 40°C and a mean spray rate of 100 g/min was used.

Non Pareil Pellets	kg	14.6
Active	kg	14.6
Binder	kg	4.9
IR Pellets	kg	33.12
Pellets agglomerated	kg	0.026

Table 1: Yield of IR beads

Sustained release coating process

Each IR pellet batch was split into three batches with 10 kg batch size each. First IR batch was coated with 95% Eudragit RS 30 D and 5% Eudragit RL 30 D, in presence of plasticizer and glidant*. The resulting pellets were very sticky and need to be separated with Aerosil. The release rate was by far to fast.

Therefore we coated the second batch with Eudragit RS 30 D only and replaced the softener and glidant. Stickiness was no issue anymore, but the release profile was initially to slow.
Both runs were done at 30°C pellet bed temperature and 75 g/min spray rate. Pellets were coated up to a polymer weight gain of approx 20%.

The fact that initially only very few amount of active releases but finally the release rate goes up very fast indicates an interaction of active and polymer (Diagram 1). With this high polymer concentration the release should be much slower. For the next batch we decided to change the polymer (use another Eudragit-plasticizer-glidant combination).
Even with the first batch we matched the desired release profile with a polymer weight gain of 7.7% (Diagram 2).
All samples were cured in an oven. For the final production process the curing – which is a tempering step after the coating, to allow the polymer particles to create a dens and closed film – should be done in the fluid bed. Regular curing in fluid bed is of about one hour and therefore very short in comparison to curing in an oven which is done normally for 24 hours. The curing was examined with 7.0% weight gain coated sustained release Pellets (Diagram 3). It could be shown that the new Eudragit needs long curing times at →

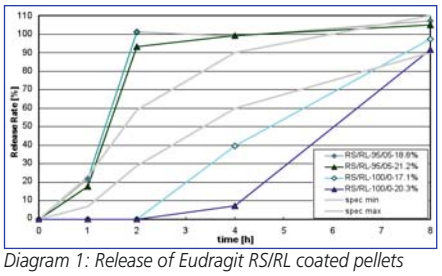

Diagram 1: Release of Eudragit RS/RL coated pellets

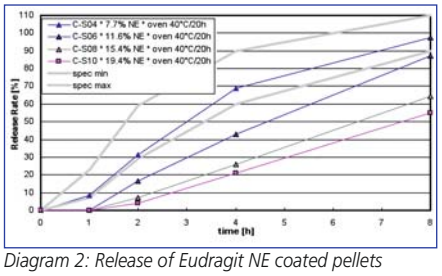

Diagram 2: Release of Eudragit NE coated pellets

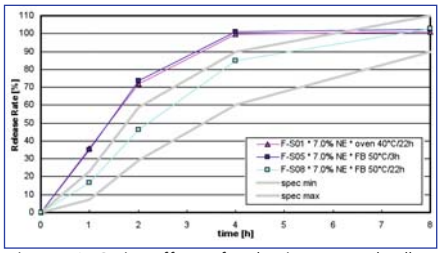

Diagram 3: Curing effects of Eudragit NE coated pellets

*Due to confidentiality agreements we are not able to name details regarding active and excipients as well as process conditions.

➔ Continuation: Pellet coating process

relatively high temperatures of 50°C. At the end we needed 22 hours curing in a fluid bed at 50°C and 10% relative humidity to be sure that the curing was completed.

Conclusions

The reformulation study was very successful. In a very short time it proved it was possible to transfer an old Pellegrini Pan coating process to a modern fluid bed coating process. At the same time most excipients were exchanged, such that the new process occurs in absence of solvents. Of special note, the fluid bed sustained release coating process resulted in a pellet bed without any agglomerates and with efficiencies of 98% and more.

In the near future this process will be established in a BFS 240 Bohle fluid bed for production. Bohle will assist in installation, qualification and validation work for the BFS 240. In addition, Bohle recommends the scale up parameter settings for the production scale process and will help guide the client through the first validation and production processes.

We would like to thank our client for this effective and cooperative collaboration as well as Formula GmbH, Berlin, for the fast and precise measurement of the release profiles. Without all the open discussions within the team, the study would not have been so successful. ■

l.b. bohle + formula

Implementation of international development and manufacturing accomplished

The 2007 cooperative between L.B. Bohle Maschinen + Verfahren GmbH and Formula GmbH located in Berlin is the basis for the newly established L.B. Bohle Formula. Pharma Services GmbH. In the recent past complex requests from international clients were successfully completed. The focus was not only the task of developing unique scientific formulations but also timely coordination and logistics of active pharmaceutical ingredients regulated by narcotic drug law.

Import and export of these regulated substances and dosage forms into other EU and non-EU countries such as the USA and Canada presents a very special challenge. Many of these dosage forms are produced at the L.B. Bohle Service Center in Ennigerloh, Germany. We address these challenges and provide the solutions with this new organization.

One particular challenge focused on the application of higher active concentrations to pellets followed by an enteric coating. The coating was designed for a timed release over an 8 hour period.

In addition to the compressed timeline determined by the complex logistics and limited authorization to handle narcotic drugs, we had to develop an HPLC-method to examine the assay of API after dissolution from coated pellets. Through successful cooperation between the participating analysts and scientists, the customer's manufacturing process was continuously improved such that the medicinal product specification was fulfilled. In the end, a robust process was created which exceeded the client's expectations. ■

BØHLE INNOVATIV
THE L.B. BOHLE CLIENT JOURNAL

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