Press Release

NETZSCH
Grinding & Dispersing

1. Dezember 2016

Scale up ensures Investment Security

Ultra-fine Grinding of Active Pharmaceutical Ingredients

Fine active ingredients are the current trend. In the development of drugs, it is therefore important that the grinding technology employed can be transferred from the laboratory to production scale. At Debiopharm Research & Manufacturing SA (Debiopharm), good experience has been gained with the use of batch mills, from which the parameters can later be carried over to the recirculation mode of operation on a production scale.

With the ultra-fine grinding of pharmaceutical ingredients, it is possible to develop medicines with new effects. Thus, the capacity of the human organism to absorb active substances is improved, opening up new areas of application. In addition, the release of the active ingredients within the body can be controlled, ultimately achieving more conservative dosing and therefore better tolerability for the patients.

The DeltaVita agitator bead mill enables the grinding of active pharmaceutical ingredients into the nanometer range. This machine, which was specially developed for the needs of the pharmaceutical industry can be used for both laboratory and production scale. A higher energy input and high throughputs ensure economical plant operation. The machines can be operated in continuous pass or circulation mode as well as in batch mode.

So, for example, initial clinical trials are run on the laboratory scale to determine whether a grinding process is generally suitable. Since, in most cases, pharmaceutical ingredients are expensive, the batch mode is typically advisable because the smallest batch sizes can be run. Compared to continuous pass or circulation operation, the batch mode stands out for its significantly lower costs. For a seamless transfer of the established process parameters to production scale in the future, the individual models can be scaled - ensuring investment security from the start.

The batch mode of operation has been tested in research and development at the Swiss pharmaceutical company Debiopharm in Martigny. In the following interview, technology specialist Julien Cotter reports on their experience.

The Author:
Sven Hoffmann is a Sales Engineer at NETZSCH-Vakumix

Photo 1: DeltaVita agitator bead mill equipped for the batch mode.

Photo 2: The small batch parts for the agitator bead mill (15-300) are used in drug development and enables a scale-up of the process parameters attained to the future production scale.

Interview with Julien Cotter, Debiopharm
"Quality by Design in the individual stages of development"

Julien Cotter is an R&D Advanced Technologies Specialist with Debiopharm
“From our experience, all particle size distributions achieved in the batch mode can be reproduced in the recirculation mode”.

How did the batch mode perform in your tests compared to the recirculation mode?
Cotter: The main advantage of the batch mode is to reduce the batch size during early development steps. The minimal batch size in recirculation mode is approximately 100 ml, while this volume is reduced to 10 ml in batch mode. Another advantage of the batch mode is the

reduction of milling time. During the milling, all the suspension is located in the milling chamber, while this is not the case with a recirculation mill. The milling process in recirculation mode with 100 ml of suspension will take approximately five times longer than a milling process in batch mode to obtain the same result.

In what ways does the batch mode affect the R&D work?
Cotter: During the early stage of pharmaceutical development, the API is generally synthesized in small quantities and the cost is extremely expensive. In this context, the reduction of batch size is a big advantage. The DeltaVita 15-300 allows us to work with the same equipment during all preclinical processing studies. We can use the DeltaVita from the initial development stages and obtain important information on formulation and process possibilities very early on. In addition, the DeltaVita 300 ml allows us to obtain scalable parameters for a transfer to the DeltaVita production series. QdB (Quality by Design) is therefore assured during the development phase (Critical Process Parameters).

How is sampling carried out?
Cotter: Sampling during milling is very important because it allows us to determine the milling kinetics and to stop grinding at the right time. Sampling in the batch mode is done by introducing a syringe through a septum in the lower part of the rotor. It is absolutely necessary to stop the rotor before sampling. As the sampling is done in the middle of grinding media, it is really important to choose the right needle size. The needle must be smaller than the grinding media diameter, but not too small - otherwise some of the particle sizes will be omitted during sampling. Once the correct needle is selected, the sample can be taken very quickly and the rotor started again to continue the milling process. From our experience, no problem with leakage has been observed during sampling.

How does the suspension recovery work in the batch mode?
Cotter: In comparison with the recirculation method, the suspension recovery is somewhat more difficult in the batch mode. The suspension and the grinding media must be recovered together and then separated. In our case, the suspension is recovered in a small glass container and separated from the grinding media with a syringe.

Are the process parameters for the batch mode transferable to the recirculation mode?
Cotter: From our experience, all particle size distributions achieved in the batch mode can be reproduced in the recirculation mode. However, it is extremely important for the scale-up that the process parameters selected are consistent with parameters used in the recirculation mode. Our experience shows a slight increase in temperature in the batch mode as compared to industrial processes. The temperature can be maintained below 30°C during milling. Here it is important to take into account the stability of the suspension if the temperature increases during the transfer from batch mode to recirculation mode.

How does the batch mode affect cleaning?
Cotter: There are fewer parts required for the batch mode compared to the recirculation mode, so the cleaning time is shorter when the batch mode is used. All of the parts used in the batch mode, except the probes, can be cleaned in an autoclave or manually. On the other hand, Cleaning in Place is not an option for decontamination with the batch mode, while it is with recirculation mode.

Is there a definite place for the DeltaVita for future development work at Debiopharm?
Cotter: Size reduction to the nano range is one of the technologies screened during the initial development phase in order to identify delivery options for poorly soluble APIs. This is part of our strategy for either oral or parenteral administration. The next step will be to prepare the scale-up phase, which will involve the DeltaVita 300 to determine CPP (Critical Process Parameters) and CQA (Critical Quality Attributes).