BATCH CASE STUDIES.

Real-World Solutions.

GEA Engineering for a better world.

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Containment Line for Anticancer Drugs.

GEA supplied a complete containment line to Ranbaxy Laboratories Limited (Gurgaon, India) to manufacture highly potent anticancer drugs with an OEL of 1–10 µg/m³. It was essential that the process prevented any cross-contamination in the production area and limited operator Real Daily Intake (RDI) values of hazardous substances to well within the Acceptable Daily Intake (ADI).

During the selection process, several key equipment features were specified:

- all units had to provide full containment
- the entire process had to be contained in a single machine to avoid contamination and limit material handling
- the technology had to be flexible enough to adapt to different products and batch sizes
- the process should provide maximum yields with minimum wastage
- there should be a clear and straightforward documentation procedure.

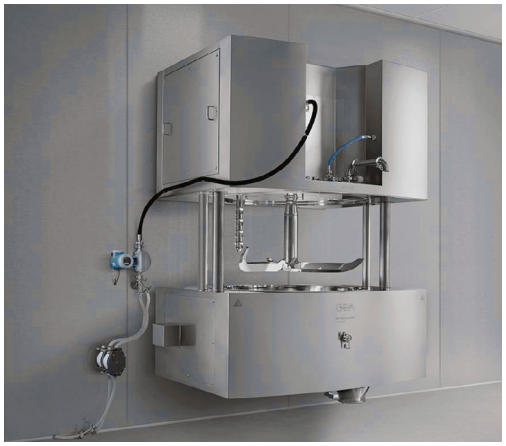
In addition, it was essential that the operators had an in-depth understanding of both the equipment and the relevant containment issues. To meet the production, containment and whole lifecycle cost requirements, Ranbaxy chose two single-pot processors from GEA: the UltimaPro 10 and the UltimaPro 75 (10 L and 75 L processing bowl, respectively).

The safe, low temperature, vacuum drying technology was augmented with microwaves or Transflo (gas-assisted vacuum drying); endpoint determination was achieved using a torque sensor (granulation) and NIR (end humidity); a built-in camera allowed operators to view the process without opening the lid; and cleaning was done by a comprehensive fully validated CIP system.

The new equipment has allowed the company to develop niche oncology products in a contained environment that protects its workforce and the wider environment from toxic compounds. Since installation, predicted levels of production, containment and operational efficiency have been achieved.

In addition, factors such as very effective microwave drying for aqueous feeds, more consistent granule sizes and much less operator intervention than had been anticipated have been cited as “areas of exceptional performance.”

Lalit Sood, Projects Director for Ranbaxy, said:
“The unit cost reduction has opened up the market and enabled the company to provide a hard-to-resist proposition worldwide. The GEA technology gives us security of outcome with the guaranteed quality and consistency we need.”



Inline Control of High Shear Granulation.

Sanofi Genzyme reduces probe fouling and improves NIR data using GEA's Lighthouse Probe.

Sanofi Genzyme was looking for a Process Analytical Technology (PAT) solution to control the high shear granulation of a formulation by measuring a critical product attribute. As opposed to relying on time-based processing or impeller blade loading, the company used an optimized Lighthouse Probe to obtain representative near infrared (NIR) data.

Genzyme's new drug was undergoing Phase III clinical trials. The active pharmaceutical ingredient (API) had a small particle size but poor flow properties. This presented the company with a challenge when formulating a dosage for patient administration. To improve the flow characteristics, the API was to be combined with excipients and processed by high shear wet granulation.

Experimental Setup

The GEA Lighthouse Probe was attached to a Bruker Matrix-F spectrometer and inserted — through a customized opening in the granulator lid viewing window — into a PMA-1 10 L granulator bowl. Using a manufacturing process design of experiment (DoE), including five high shear wet granulation-related factors, 20 batches were analyzed.

NIR spectra were collected from the granulation process at a scanning speed of approximately one spectrum every 5 seconds. The last six spectra collected from each granulation step were averaged and correlated against granule attributes such as water content, particle size and density of the final blended product.

The wet granules were subsequently tray dried, milled and blended with a lubricant. Principle component analysis was done throughout the granulation process to assess any changes taking place.

Conclusions

The Lighthouse Probe showed that it is well suited to monitoring a high shear wet granulation process when used as the sample interface with an NIR spectrometer (Figure 1). It minimizes probe fouling — based on its 360° window — and allows for the maximum absorbance of light from the spectrometer, which facilitates signal detection.

The Lighthouse Probe enabled satisfactory models to be produced for key granule attributes such as water content, particle size and bulk tapped density. This study proved the viability of Lighthouse Probe technology to monitor and control a high shear wet granulation process.

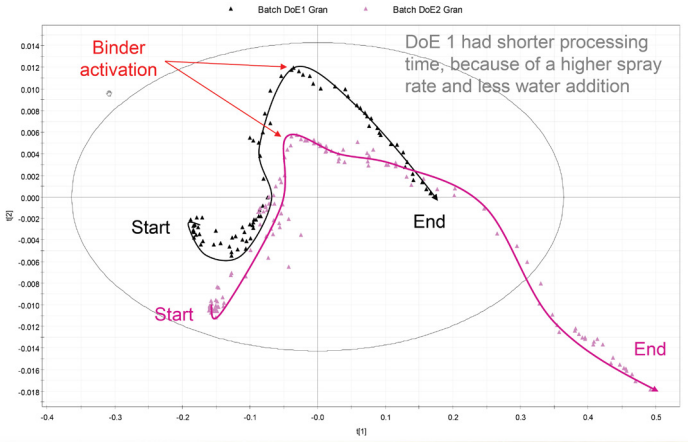


Figure 1: A Hotelling's T2 plot shows that the process time for the first batch was shorter than second batch because less water was added at a higher spray rate. The plot inflexions could be related to the point at which sufficient water is present to activate the binder in the formulation.

Fully Integrated and Contained Tableting.

After conducting extensive market research, Penn Pharma (now PCI Pharma Services) identified an increased need in the solid dose oncology market for the outsourced development and production of high quality, highly toxic drugs. Initiating an investment project to upgrade its site capabilities to support this market need, the aim was to create a new multiple active pharmaceutical ingredient (API) facility that could produce 1–120 kg batches using full containment according to ISPE guidelines.

Its production site had been manufacturing potent solid dosage products for more than 20 years but needed additional capacity. Without both innovation and investment to provide better solid dosage technology, and dispense with the cumbersome isolation suits that restricted development and were uncomfortable for operators, Penn would not be capable of achieving the production levels required by international pharmaceutical companies and business would only grow at the same pace as the global outsourcing market.

To take advantage of the opportunity identified by its research, Penn would require a totally new concept in plant design that embraced leading technology, the latest techniques and the ability to upscale operations from research and development, through pilot-scale testing up to full production, all under one roof.

Penn Pharma elected to work with GEA because of its proven track record in containment technology and expertise in creating fully integrated production lines. GEA's approach was to eliminate the use of isolation suits in favor of containment interfaces (BUCK® MC high-containment valves and Hicoflex®).

These would not only interface with GEA's advanced granulation, containment and compression technologies, but also with third-party equipment such as the powder dispensing isolator and, further downstream, the tablet filling and tablet coating elements to produce a fully contained, powder-to-capsule facility in an open working environment.

The new plant now includes the first commercial "through the wall" PharmaConnect system in Europe. The contained R&D line for wet granulation also includes the dispensing of excipients and potent powders, GEA's PMA 150 and FlexStream 1000 for granulation and drying, dry milling, granule collection and blending, tablet compression using a MODUL P tablet press with a Wash-off-Line ECM (exchangeable compression module) and pellet coating.

The plant also has a contained R&D line for direct compression and a separate production line that offers containment interfaces for powders, API and excipient dispensing, dry milling and powder collection and blending.

Penn Pharma is now a single source for the development and production of highly toxic drugs at one of the world's most advanced and efficient facilities. The project has significantly increased their capacity and the company can now manufacture approximately 500 additional batches during a standard two-shift operation.

Project Objectives

Safety: The facility was designed to handle multiple APIs with occupational exposure limits (OELs) down to 0.01 µm/m³, based on an 8-hour time weighted average (TWA). The approach was somewhat unconventional, as it started with a negative pressure equipment philosophy that would eliminate the need for personal protective equipment in routine operations.

Quality: The new contained manufacturing operation had to meet the regulatory needs of the global markets supported from the site, including the US, Japan, South America and Europe.

Delivery: The facility was designed to be flexible enough to support customers through development, early phase and commercial supply. It had an accelerated timescale and aimed to turn a car park into an operational facility in 12 months.

Cost: Nothing could be compromised on quality or safety; successful equipment sourcing was key. A robust FMEA selection process and commercial bid analysis was done to secure cutting-edge equipment at a competitive market price.

People: With an initial team of five project members, supported by an external project design and construction team, the focus was on speed to market. Armed with a full complement of formulation, quality, validation, engineering, regulatory and operational skills, and budgetary control, everything was put in place to create a unique, market-leading facility.

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