

INDUSTRY

application

Gravimetric feeders support Eli Lilly's advancements in continuous direct-compression tableting

Continuous direct compression (CDC) tableting offers several key technical and process advantages over traditional batch tableting processes. First and foremost, it allows the manufacturer to develop a drug product on the same equipment drivetrain that will be used for the product's final manufacture, eliminating process scale-up. CDC tableting also allows for increased quality assurance and requires less production space, which lowers utility and labor costs.

In continuous processing systems, active pharmaceutical ingredients (APIs) and excipients must be delivered continuously at the proper proportions to ensure the quality and efficacy of the final drug product. As a result, feeding accuracy and consistent refill of the feeders are critical. A CDC line typically includes individual feeders for the API and excipients feeding directly into a blender, with the blended formulation discharging directly to the tablet press. Each feeder can be continuously refilled via an automated system to ensure consistent material flow during the continuous process.

Gravimetric versus volumetric feeders

In principle, process designers have a choice between volumetric feeders, which discharge a specified volume of

material per unit time, and gravimetric feeders—also called loss-in-weight (LIW) feeders—which discharge a specified weight of material per unit time. Volumetric feeders are simple and inexpensive and can be useful in non-critical applications, but they have no way of detecting or responding to changes in the bulk density of the material they are handling.

On a gravimetric feeder, the hopper and feed screw are mounted on a scale or load cells. During operation, as material discharges from the feed screw, the feeder's control system continuously monitors the

weight of the feeder and its contents. The system immediately detects any changes in the feedrate—whether caused by a change in the material's bulk density or other factors—and automatically adjusts the feed screw speed to almost instantly restore the correct feedrate.

Pharmaceutical applications, such as CDC tableting, require consistent and highly accurate feeding of ingredients that commonly have extremely poor flowability and require very low feedrates. The gravimetric feeder's closed-loop mode of operation makes it ideal for such applications. In addi-



Photo 1: The continuous direct compression suite including gravimetric feeders is mounted on a custom lift assembly to ease access, cleaning, and product changeover.

tion, the control system has real-time access to information about the true delivery rate and can make this information available to external systems as an aid to enhancing traceability and quality control.

Several years ago, Eli Lilly and Company (Lilly), headquartered in Indianapolis, IN, was developing several CDC tableting lines for Verzenio, a targeted, breakthrough treatment option for metastatic breast cancer. To source the critical gravimetric feeders for these systems, the company partnered with Coperion K-Tron, a global supplier of processing and handling equipment to the pharmaceutical, plastics, chemicals, food, and minerals industries.

"Many factors influenced our decision to specify feeders from Coperion K-Tron," said Joshua Hanson, consultant engineer at Lilly. "We knew that the company's products have an excellent reputation for accuracy and that their robust construction would ensure a long, reliable working life in a manufacturing environment. The modular design was also important to us, as it permits flexible system configuration and reconfiguration."

Feeder performance and product quality

Not all gravimetric feeders are capable of the performance required in CDC applications. Characteristics such as the load-cell resolution and long-term stability, control algorithms, and the linearity of the system that relates the feed screw speed to the measured flowrate all have a major impact on the feeder's overall performance and must be carefully considered, even when choosing among nominally similar gravimetric feeders. This was particularly true for Lilly's CDC systems, where control of feeding operations was to be a primary element of the quality control strategy used to ensure that drug critical quality attributes were achieved.

Achieving reliable feedrate control for CDC systems can be particularly challenging because of material variations and the low flowrates that are frequently involved. While equip-

ment such as mixers downstream from the feeders can be used to compensate for feeding variations, this reduces productivity and is only feasible for short-term variations, since systemic feeding errors over longer time periods cannot be blended out. In practice, successful implementation of CDC systems ultimately depends on feeder performance.

"The Coperion K-Tron control architecture not only allows easy integration with our DeltaV distributed control system but also supports ratio control, where feeders are linked so that subordinate feeders respond rapidly to changes in the master feeder's mass flowrate, thereby keeping the ratio of ingredients constant," said Tim Pletcher, senior consultant engineer at Lilly. "We find this feature an invaluable aid to minimizing the impact of disturbances caused by, for example, feed hopper refilling."

It's important to note that disturbances can still occur in any manufacturing environment. Addressing these disturbances requires a robust mitigation system and strategy. According to Hanson, "Coperion K-Tron has responded to these challenges by improving their technologies and offering options such as vibration filtering, mechanical and electronic compensation, and a data rich out-

put to allow for process monitoring, including signal-to-noise ratios and feeder performance diagnostics."

Cooperative system design and implementation

The project and process engineers at Lilly and Coperion K-Tron worked together closely during the design and implementation phases of Lilly's three CDC installations. Making the process design particularly challenging was the frequent need for the feeders to operate at very low feedrates delivering materials with poor flow characteristics. The supplier offered a flexible and responsive approach to customizing the software and control packages, giving the Lilly development team wide scope to explore solutions that would optimize the CDC system feeding operations.

The companies' close cooperation proved particularly valuable in developing suitable designs for two of the three CDC lines where it was necessary to retrofit vertical arrangements of clustered feeders into existing facilities with severe space constraints. The designs also included an innovative lift system that supports the main process train and feeders, allowing for ease of access, cleaning, and product changeover. During the implementation phase, Coperion K-Tron engineers were on site to help ensure a



Photo 2: Multiple upper-level gravimetric feeders discharge ingredients continuously into a blender on the level below. The feeders are mounted on specialized pivoting tracks to optimize accessibility.

smooth installation, commissioning, and qualification process.

Improved quality, efficiency, and flexibility

In September of 2017, the FDA approved Verzenio, making it one of the first FDA-approved drug products manufactured using a continuous process. Since then, Lilly has been operating its CDC systems long enough to form a clear picture of the benefits they provide, which include enhanced quality assurance, financial savings, operational efficiency gains, and increased flexibility.

The CDC systems use a progressive control scheme anchored by advanced automation and process analytical technology (PAT) to ensure consistent control, low process variability, and high quality assurance. Replicating the CDC facilities across all three of the company's lines has reduced the development and technical transfer time needed to start the commercial manufacture of early-phase treatments in the Lilly pipeline.

"Greater implementation speed has proved possible because the process scale, equipment design, and automation infrastructure are virtually identical for all three plants," said Hanson. "This means that process scale-ups were eliminated, technology transfer risks reduced, and development costs were far lower than those of more traditional operations. CDC also brings supply chain flexibility by enabling the production of flexible batch sizes. This allows easier transition from smaller batch sizes used to supply clinical trial demands to the larger batches needed for full-scale commercial supply."

As a result of Lilly's dedication to process innovation, the company won the prestigious International Society for Pharmaceutical Engineering (ISPE) "Facility of the Year" award in 2017 for its Indianapolis and Carolina, Puerto Rico, facilities. The awards were in the categories "Facility of the Future" and "Process Innovation" and were based on the design and performance of the complete CDC systems, recognizing

Lilly's forward-looking stance and positive attitude toward innovation.

As the Lilly systems demonstrate, continuous manufacturing of oral solid dosage forms has begun to impact the quality and efficiency of pharmaceutical manufacturing. According to Hanson, "The end result is that not only can the company deliver novel therapies quicker, but it can also focus on producing more cost-effective therapeutic treatments that will make life better for patients." *T&C*

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