Continuous Tableting: From Powder to Tablet in 20 Minutes

Now that two key hurdles have been removed, and a new generation of equipment has been developed, the future looks bright for continuous processing in tablet production.

Tablet presses have always operated continuously; however, up until now, they have mainly been used in a batch mode operation regime. There are two main reasons for this: first, the equipment supplying the granules to the press were batch processes; and second, restrictions exist in the regulatory environment. Both of these hurdles to using a tablet press in a continuous fashion have been removed in the last couple of years.

The US FDA has been promoting continuous processing as a method to improve quality in pharmaceutical production since the publication of its Process Analytical Technology (PAT) Framework in 2004 (1). In recent years, FDA speakers have delivered presentations at numerous conferences and seminars, discussing the advantages of continuous processing using the Quality by Design (QbD) and PAT philosophy. According to the FDA, manufacturing without interruption with a constant flow of materials fits very well within the concept of QbD. It provides many opportunities to adjust the process to meet the critical quality attributes and thus patient safety (2).

Continuous equipment for the production of pharmaceutical granules is not new; it has been around for many years (often adapted from equipment for the food or chemical industry). These early systems, however, had major drawbacks that made them impractical for the pharmaceutical industry. Many had high waste at start-up and shut-down, making them only suitable for relatively low-cost products that required a high volume production. R&D on these systems was often difficult; the systems had issues with plug flow, were not easily cleanable and could not be used as flexible R&D equipment.

A NEW GENERATION

A new generation of continuous production equipment overcomes these problems and ensures no – or only minimal – waste at start-up and shut-down. GEA’s ConsiGma™ continuous tableting line was developed in concurrence with the FDA’s QbD initiative and was designed to satisfy the industry’s need for continuous production to provide improved quality, flexibility and consistency for pharmaceutical processes. The systems are designed in such a way that both R&D and production can use the same size of equipment, thus eliminating scale-up. Further advantages are a higher yield and very stable, plug flow-based processes leading to increased quality levels and higher efficiency. In addition, development...
times are shorter, the total cost of ownership is reduced and energy consumption is lower. So far, more than 50 companies have tested over 80 different formulations at the GEA Competence Centre in Belgium.

One system can run 500g in R&D, but can also run clinical trial, launch and production size batches. As there is no process scale-up – time is the only relevant factor in a continuous process – manufacturers are able to reduce development time dramatically, thereby reducing costs and bringing products to the market much faster.

At one-third of the size of a classic granulation line (inclusive of a tablet press), the system is very compact, while its modular construction allows it to fit perfectly into any R&D department or existing tablet production room. There is no need for any building alterations – the system is just wheeled in, connected to the power and air supply, and after a simple start-up period is ready to go. Installation time and cost are reduced to a fraction of the current benchmark. It is also possible to avoid high peak energy periods and run at continuous low energy consumption, helping companies meet their environmental obligations.

The ConsiGma™ system is capable of undertaking particle design and mimicking any traditional batch granulation process – with a much higher and consistent quality resulting from its continuous production set-up and ‘risk-based approach’ to GMP. The granules have generally a better intra-granular porosity, with improved compressibility characteristics that help tablet presses run more efficiently at maximum speed with hardly any weight adjustments being required.

The full tablet production line consists of the ConsiGma™ high shear granulator and dryer, combined with a GEA Courtoy MODUL™ P rotary tablet press. A special in-line blender mixes in the external phase between the systems. The granulator and dryer section of the line has three modules: a wet high-shear granulation module; a segmented dryer module; and an evaluation module.

In the granulation module, dry ingredients are dosed – either individually or premixed – in the continuous high-shear granulator. After a dry-mixing section, the granulation liquid is added, so each particle receives the same amount of liquid.

The dryer module, based on fluid-bed drying principles, splits the continuous flow of granules into packages of 1.5 kg, drying each of them in a separate segment of the dryer and thereby guaranteeing plug-flow. When each segment is dry, it is emptied and transferred to the evaluation module and refilled with a new package of wet granules. The drying curve of each package is monitored as a fingerprint of the process, and controlled to maintain a constant end-humidity over the whole batch.

In the evaluation module, the dried granules can be measured for critical quality attributes such as particle-size distribution, humidity and content uniformity, using specially designed PAT tools.

The MODUL™ P rotary tablet press is based on the innovative Exchangeable Compression Module (ECM) concept. The ECM is completely isolated from the remainder of the machine, contains all product contact parts, and can be removed easily from the press in a contained way. This means that the press itself remains powder-free and requires no cleaning. The six compression modes available in the press make it ideally suited for this continuous tableting line, allowing easy R&D and perfect production, with dual control for independent weight and hardness control, and equal porosity tableting. The constant dwell time regardless of throughput fits perfectly in a continuous line because it enables the press to change its speed when necessary – for example, when a sample is taken in between drying and tableting.

REAL-TIME QUALITY ASSURANCE

The development of on-line measurement techniques is another important factor in the success of continuous processing. One of the reasons pharmaceutical companies stick with batch production is the fact that
they can easily define the amount of product that needs to be rejected in the case of ‘out-of-spec’ results. Their biggest fear with continuous production is that they will not be able to determine which product generated the out-of-spec result, and so they would have to throw away the whole campaign (which could last days). However, with the development of on-line measurement techniques, it is very easy to track the product continuously and reject any out-of-spec product at the very moment it is detected, before it can ‘contaminate’ the whole batch.

Also, the advanced control systems now available allow for feed-back and feed-forward loops that will automatically adjust the process parameters to correct any change in the critical quality attributes (even before the product becomes out-of-spec). Some pharmaceutical companies are starting to develop a real-time release philosophy, where the product will be released immediately after production – based on the online analyses – and the product will no longer be tested in the analytical lab.

Real-time assurance involves control mechanisms and process measurements to ensure that the process has continuously operated within the design space that is known to deliver product or tablets of suitable quality. Real-time release is a systematic, scientific, risk-based approach. As the product-release decisions are made as close as possible to the time the product is manufactured, it is essential to employ advanced process control, use robust online process analytical technologies and have fundamental process understanding to guarantee reaching the objectives.

**FDA SYMPOSIUM**

The value of continuous manufacturing was reviewed at a recent internal US FDA symposium aimed at educating personnel about the latest developments in this technology. As well as FDA staff, three speakers from leading universities were invited, two presentations came from Big Pharma (Pfizer and GSK) and, as the only manufacturer of process equipment present, GEA Pharma Systems also participated with a presentation.

In his introductory presentation, the Chairman highlighted the fact that, in the view of the FDA, the use of continuous processing in pharmaceutical production will lead to an improvement in product quality. A further presentation on behalf of the FDA focused on the benefits of continuous manufacturing such as: easy or no scale-up, flexible batch size, fast development with less product, and constant quality and so enhanced patient safety. The importance of plug flow in such processes was also stressed.

The GEA presentation reviewed the various control philosophies within the ConsiGma™ line – ranging from traditional fixed recipe control, via advanced process control with integrated feed-back loops (enabling compensation for fluctuations of, for example, incoming materials), up to Real Time Release (as all Critical Quality Attributes (CQAs) can be measured in-line and at a much higher frequency than would be possible with any batch process). Two aspects of the continuous processing approach that were particularly well-received were the assurance of plug flow over the entire process, and the increased number of measurements of CQAs, as confirmed by data from an uninterrupted 50-hour run resulting in 1.8 million tablets. During the 50-hour test, more than 960 in-line measurements were taken to determine CQAs such as Loss in Drying (LOD) or particle size distribution, while the content uniformity of the final tablets was assessed in-line more than 100 times.

**CONCLUSION**

In recent years, the adoption of continuous processing in tablet production has been hampered by, first, the supply of granules in batch mode, and second, regulatory restrictions. With the recent advances in technology and the endorsement of continuous processing by the US FDA, these hurdles have now been removed and the future for continuous processing in tablet production is looking extremely bright.

**References**


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