Increasingly, pharmaceutical production plants must be efficient and user friendly. They must also meet industry demand for shorter development times with minimal active pharmaceutical ingredient (API) usage and direct transfer from development to production without scale-up, as well as flexible batch sizes and integrated quality monitoring. This article discusses how continuous manufacturing technologies can help drug product manufacturers meet these requirements.
trend toward highly potent active ingredients and more personalized drug products will also influence production and process requirements, leading to smaller and more flexible production quantities with the shortest possible time to market.

For many decades, the pharmaceutical industry has manufactured SODFs using traditional batch production processes. To a great extent, these processes have already been optimized and offer little opportunity for significant further efficiency improvements. As a result, large and medium-sized pharmaceutical companies have recently turned their attention to continuous processes, which have long been used in other industries, such as chemical manufacturing. Generic and contract pharmaceutical manufacturers are also increasingly interested in continuous processing. Against this background, a paradigm shift is taking place in the pharmaceutical industry that will fundamentally change the infrastructure and internal processes of SODF manufacturers.

**From batch to continuous manufacturing**

In batch production, a set amount of raw material is fed into each process step and the same amount is removed at the end of each process step, resulting in non-value-added charging and discharging operations and requiring additional plant space to store the material between steps.

In continuous manufacturing, the process steps occur one after the other without interruption, so the raw materials are fed into the system and the finished product is discharged from the system simultaneously. This results in shorter throughput times and eliminates the need for intermediate storage, reducing production costs and plant-size requirements and allowing for greater production flexibility.

With continuous manufacturing, production volume is controlled via the production time. Scale-up becomes obsolete, which reduces development costs and time and API usage. Continuous manufacturing processes also offer optimized quality monitoring, which ensures consistently high product quality.

The value of changing from batch to continuous production depends on a number of factors, including the active ingredient, the production amounts required, and whether the product has already been approved or is still in development. Pharmaceutical manufacturers should discuss these factors with their equipment suppliers, as the costs and benefits vary on a case-by-case basis.

**Continuous pharma’s current status and challenges**

Continuous manufacturing is not new to the pharmaceutical industry. Even in batch production, some of the individual processing steps operate in a continuous manner, such as dry granulation using roller compactors or tableting. Other processes, such as dosing, mixing, and wet granulation operate in batch mode and must be modified for continuous production.

Current continuous production systems for wet granulation usually rely on continuous twin-screw granulators, with the subsequent fluid-bed drying usually occurring via a package-per-package approach in separate chambers, to control the material’s residence time and expose all the particles to the same amount of drying energy.

The biggest challenge for today’s continuous production systems is precisely dosing the starting materials. Systems must continuously dose active ingredients and excipients at constant mass flow rates in the range of milligrams per second. Because all currently available dosing systems exhibit fluctuations in the achievable mass flow rate over time, it’s mandatory to check the API content online using process analytical technology (PAT). Back mixing is the only way to compensate for these flow rate fluctuations, but this broadens the material’s residence time distribution in the system, making traceability more difficult. In addition, current continuous systems require a startup phase before achieving steady-state operation, which results in startup and shutdown losses.

Another challenge of continuous processes that include twin-screw granulation is that the granularity density can change over time and the material often has a bimodal particle-size distribution. This might cause particle-size segregation, which can have a negative effect on tablet properties in certain circumstances and is something that manufacturers should consider when transferring technologies.

As these challenges show, continuous pharmaceutical production still has room for improvement. However, new technologies such as Bosch Packaging Technology’s Xelum platform are demonstrating that these challenges can be overcome.

**Reducing complexity**

One solution to improve dosing accuracy is to dose APIs and excipients as discrete masses rather than using continual mass flow. This allows precise dosing of even the smallest API amounts. The system doses and mixes the ingredients in individual packages, which continuously run through each step of the process chain and are removed successively. This reduces both the process complexity and the system’s susceptibility to failure, which increases the consistency and quality of the end product.

This also makes it easier to measure the necessary critical quality attributes, in part, using soft sensors. Because the system does not require steady-state operation, startup and shutdown losses are eliminated. All starting materials can be traced back along the production line and clearly matched to the final dosage form, as back mixing occurs only within each individual package.

**Advantages of fluid-bed technology**

Continuous systems can avoid the challenges associated with twin-screw granulators by using flu-
id-bed processing instead. In a fluid-bed processor, granulation and drying can occur in the same process chamber, eliminating the need to transfer wet granulated material and improving system reliability. Fluid-bed granulation allows manufacturers to achieve unimodal particle size distributions, excellent flow and tableting properties, and higher production yields. Using the fluid-bed granulation process for existing products also eliminates the need for technology transfer, which makes changing from batch to continuous processing significantly easier.

Systems can apply the same principle of dosing as a discrete mass to the external phase. In the final processing step, tableting takes place in an integrated tablet press. Connection to line controls and a flexible filling-height control ensure smooth operation, while wash-in-place (WIP) nozzles ensure fast and largely automated cleaning.

**Fit for the future**

Transferring traditional batch processes such as the top-spray process from the laboratory to production is often a challenge for pharmaceutical manufacturers. Continuous processing eliminates this inherently risky and time-critical stage. Manufacturers can develop new products using suitable R&D equipment or a continuous platform such as the Xelum system that features an integrated automatic design of experiments (DoE) function and software equipped with the relevant test-automation support functions.

Continuous SODF manufacturing will take on an important role alongside batch production. Manufacturers must decide which method to use on a product-by-product basis, keeping in mind that not all continuous processes are the same. Platforms such as the Xelum system are not limited to wet granulation and tableting but are also conceived for applications such as direct compression tableting. These systems offer an industry-4.0-ready, economical alternative to batch production and are constantly being refined to meet future industry requirements.  

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