Continuous Granulation - Opportunities to Increase Efficiency in Pharmaceutical Production

The mixture includes active ingredients and excipients (fine powders). These ingredients undergo granulation and agglomeration, while keeping a homogeneous particle size distribution. The changes in physical properties, such as better flow behavior, compressibility, low dust formation and, possibly, optimised release profile of active ingredients, favor the subsequent tableting. The changes also render the tableting possible.

In pharmaceutical production, individual process steps are traditionally executed in subsequent batches. This is also true of granulation.

Large vertical mixers are often used and agglomeration takes place inside the vessel by adding the granulating liquid and using fast-rotating agitators and choppers. For a required throughput, these devices have a narrow optimal working point. Thus, for process development, all the way from research and development to production scale, a significant number of scale-up steps have to be performed. These are often considered difficult and risky [Serno, Kleinebudde, Knop 2007]. Moreover, the yield of pharmaceutical batch production often lies in the vicinity of about 30% OEE [Overall Equipment Effectiveness, Vervaet 2005]. This could be increased through the application of continuous production technologies that have already been established in other industries such as, fine chemicals and food.

The process described here can be continuously operated, from mixing of the starting powders to the packaging of the final tablets. The process focuses on the continuous granulation of powder mixtures by using a twin-screw extruder and subsequent drying in a fluidised bed system. Since the entire process is modular, the critical process steps are relatively easily scaled-up and, one can set up facilities for development (approx. 1 kg/h) to the production scale (approx. 300 kg/h). [Figure 1]

**Granulation Using a Twin-Screw Extruder**

In this process, a Thermo Scientific Pharma 16 TSG, with two co-rotating, parallel and partially overlapping screws of 16mm diameter (D) and length (L) to diameter ratio of L/D = 40/1 is being used. [Figure 2]

![Figure 1: Continuous granulation process](image1)

![Figure 2: Thermo Scientific Pharma 16 TSG](image2)

By using an extruder for the granulation process, several steps of a classical batch granulation can be carried out in a single device. The screw shafts can be equipped...
with differently-shaped screw elements, which are able to meter, mix or granulate the powder mixture. [Figure 3].

The feeding of the individual powder components, as well as the granulation liquid, is carried out with dedicated, gravimetric feeders. This allows omitting an upstream (batch) mixing process and reduces the possible loss of expensive active ingredients. In addition, the segregation of a premix by storage or transport is also excluded.

After introducing the granulation liquid, agglomeration of particles takes place by shear forces between the screw and the extruder barrel. By utilising a suitable screw design and precise control, the process parameters of the extruder granules are produced. These have a defined particle size distribution (small content on under- and oversized particles) and are ideal for further processing in a tablet press. To avoid unnecessary compacting of the material, the extruder is operated without nozzle or die at the end of the barrel.

The advantages of using an extruder for granulation are:

- Large adjusting range of the throughput, e.g. 1 to 15 kg/h with the same extruder possible. Allows efficient process development and small-scale production.
- Very short residence times (8–15 sec), thus very low drug demand (cost savings)
- True, continuous process, which enables rapid process development and precise control.
- Low space requirements both for development and production machines
- With a few scale-up steps production rates increase up to 300 kg/h per machine

- Use of robust PAT instrumentation for process control possible

**Drying in the Fluidised Bed - Continuously**

The material exiting the extruder is dried in a ProCell LabSystem with GF5 insert (Glatt GmbH) to the required residual moisture. Due to its special design, a plug flow is created in the GF5 insert, which moves in a circular manner through the system. Through adjustable weirs and precisely-controlled process air, the residence-time can be adjusted precisely, ensuring that uniformly-dried granules with suitable residual moisture are available at the outlet of the dryer.

Ideally, the combination of the extruder and fluid bed dryer can be operated in the throughput range of 1 to 15 kg/h. Thus, on this system, a process development is possible, as well as a small production of up to 360 kg per day. For productions with higher throughput needs, both technologies, extrusion and dryer, can be adapted by using machines with higher performance. [Table 1]

**Tableting**

Some formulations need the addition of other excipients and lubricants (e.g. magnesium stearate) before being compressed into a tablet. These are metered gravimetrically into the continuous granulation process after a dry-milling step and homogenized with the granules by means of a continuous paddle mixer. The tableting step concludes the process, but it is possible to directly connect the final packaging in blisters, bottles or boxes.

**PAT**

In contrast to the final batch analysis for the product release, the continuous process has to be monitored in real-time, in order to guarantee operation in steady-state. Here, the process analytical technology (PAT) plays a major role. As described in the FDA guidance [www.fda.gov], the use of PAT serves the immediate release of the product. This enables faster time-to-market, as final and time-consuming inspection and evaluation of the respective analysis can be performed.

The process of continuous granulation, as described above, provides the opportunity for robust process on-line analytical technologies to be used at various critical process points.

For example, a NIR probe can be used directly in the extruder barrel [Figure 4] to monitor the homogeneity, residual moisture and particle properties of the resulting granules.

In the fluidised bed microwave and laser diffraction, sensors have proven to be a reliable way to determine the particle size distribution the residual moisture. All gravimetric feeders used in the process

**Table 1: Scale-Up of Continuous Granulation Process**

<table>
<thead>
<tr>
<th>Throughput (Kg/h)</th>
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<th>Throughput (Kg/h)</th>
<th>Throughput (Kg/h)</th>
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</thead>
<tbody>
<tr>
<td>0.2–15</td>
<td>10–120</td>
<td>100–250</td>
<td>250–500</td>
</tr>
<tr>
<td>2.350</td>
<td>1.000</td>
<td>1.500</td>
<td>2.300</td>
</tr>
<tr>
<td>1.000</td>
<td>1.000</td>
<td>1.200</td>
<td>1.300</td>
</tr>
<tr>
<td>2.830</td>
<td>2.500</td>
<td>2.800</td>
<td>3.500</td>
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</tbody>
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**Thermo Scientific Pharma Twin-screw Granulator**
constantly monitor the signal of the high-precision load cells for controlling the dosing and as an overarching parameter of the entire process.

In the tablet press, coupled measurements of compaction pressure and NIR signal are established technologies to ensure the quality of each tablet. If a defective tablet is identified, it can be blown-out by a directed air stream, thus 100% control is realised.

The Know-how Makes the Difference

The continuous granulation process can be used for the production of tablets from mixing of the raw materials all the way to the packing of the final drug. It is important to meet the respective process requirements by utilising modular and coordinated components. This enables the yield of classical batch production to increase significantly. Established PAT instrumentation helps in the development and operation of the process. Moreover, it can reduce “time-to-market” for a product significantly.

Important for the successful implementation of such a project is the know-how of the involved parties. Thermo Fisher Scientific and Glatt GmbH are offering the ideal prerequisite to achieve the specific customer requirements.

Reference


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GlaxoSmithKline Pharmaceuticals Limited Announces Launch of Two Drugs

GlaxoSmithKline Pharmaceuticals Limited today announced the launch of two drugs Revolade® and Votrient™ at a press conference held in Mumbai. Both the drugs are targeted towards specific patient categories.

Revolade® (Eltrombopag) is approved for the oral treatment of thrombocytopenia (reduced platelet count) in adults with the blood disorder chronic immune (idiopathic) thrombocytopenic purpura (ITP).

It is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy. It should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. It should not be used in an attempt to normalize platelet counts.

Announcing the launch of Revolade®, Dr. Hasit Joshipura, Vice President South Asia & Managing Director, India, said, “Revolade® is the first and only oral platelet generator. It is an innovative step forward in helping patients and their physicians meet the challenges of managing chronic ITP. Clinical trials have shown that eltrombopag is able to stimulate the production of platelets and reduce the risk of bleeding in this difficult to treat disease.”

Votrient™ (Pazopanib Hydrochloride Tablets) is indicated for advanced renal cell carcinoma (RCC), the most common type of kidney cancer. Speaking about Votrient™, Dr. Joshipura added, “Votrient™ approval in India is based on the results from a pivotal Phase III study of patients with advanced kidney cancer who had either received no prior drug treatment, or had failed a cytokine-based treatment. Votrient™ has been proven to significantly delay the progression of advanced renal cell carcinoma while maintaining patients’ quality of life, when compared with placebo.”

Both the drugs will be marketed by the Oncology division of GlaxoSmithKline Pharmaceuticals Limited.