More flexibility for production of **solids**

Agile systems for the **granulation process**

DIOSNA
LINXIS GROUP

The world of OSD manufacturers has changed:

Smaller and changing quantities, more specialised and different products have to be produced more frequently in their plants in ever faster cycles. The granulation process therefore now places higher demands on flexibility of plant technology than it was just a few years ago.

- **Well-thought-out scale-up** clears the way for a **flexible concept**
- **Modular design** for laboratory and pilot plants
- **Tool-free exchange** of modules supports **fast machine changeover** to different processes
- **Adaption** of the machines **to different technologies**
- **Rapid Change (RC)** between different bowl and batch sizes are feasible

Fast and safe changeovers in pharmaceutical plants require, among other things, maximum efficiency in change-over time and short cleaning cycles. Production systems that can map different processes and whose modules can be changed without tools are advantageous here. Using granulation as an example, one can show how flexibility can be implemented in practice.

Wet granulation and subsequent drying in fluidised bed systems have become indispensable in the production of solid dosage forms. After all, the mixture is optimally prepared for subsequent tabletting or coating. Granulation is also crucial because it is here that the product properties such as density, particle size distribution, flowability, compressibility, surface properties and release profile are set. In addition to the actual active ingredient, fillers such as lactose, mannitol or cellulose, binders such as starch, hypromellose or povidone, as well as disintegrants can be incorporated. For the patient, this is noticeable in a higher bioavailability or better homogeneity even with low-dose mixtures.

Mapping of **different process steps**

For the granulation of pharmaceuticals, high-shear mixing and fluid bed processes are used, among others, because they are very flexible. This is reasoned by a very wide range of designs and configurations in which several process steps are integrated such as drying, granulation or coating. These can also run in parallel. For this purpose, the systems are equipped with exchangeable bowls that are used for different process steps, such as mixing, drying, coating or filming. Tool-free changeover of the modules, options for containment or the connection of automatic feeding or dischrarging, air conditioning or solvent operation facilitate the changeover to different products and batches.

Basis is laid in **Scale-up**

With flexible systems, it is possible to switch between different technologies at a relatively early stage of development.

However, this can only be achieved if there is a straightforward scale-up concept. This is a basis for a smooth transfer of the processes to production scale. The most important aspect here is the geometric similarity of all bowl designs. For example, in mixing bowls, the ratio between diameter and height must be identical in all sizes in order to enable mathematical calculation of process parameters (e.g. via Froude number). Nevertheless, not all physical parameters can be scaled up or down at will. The step in a scale-up of a plant should therefore be a maximum of 1:10, whether it is mixed granulation, a single-pot process or fluid bed granulation. If larger steps are chosen, the uncertainties increase. Thus, inaccuracies creep in again and again during scale-up, the effects of which, however, only become apparent later in production or in quality control. Modular systems help to avoid these inaccuracies, especially in the early stages of development. Transferred to mixing granulators, this means: For product development in the laboratory, mixers with a volume of 0.25 to 10 litres have proven their worth. So if a 6-litre container is chosen here, a 60-litre volume is selected for scale-up, for example for the production of clinical samples. Production can then start with 600 litres.

Identical bowl geometries are indispensable for reliable scale-up. The same design of mixing bowls allows reliable transferability from laboratory scale to production. Diosna mixers have the same design from the smallest vessel (0,25 l) to the vessel for production (1250 l).

Increased flexibilty with a wide range of batch sizes: Rapid Change of bowls illustrated by DIOSNA's fluid bed processor **CAP 10-80 RC**

P1-6 Pharmaceutical mixer

Good start in the **lab and pilot phase**

For the later process the basis is laid already at an early stage. The leap into later production is all the easier if the laboratory or pilot plants also resemble the later process plant. Here, laboratory plants in a modular design offer the possibility of trying out different products and technologies and adapting the bowl sizes accordingly. Machines that cover a wide range of processes accelerate the workflows in this phase.

The MiniLab RC laboratory system from Diosna was specially designed for the work in research and development. It covers a wide range of processes from drying to powder, pellet or tablet coating and spray granulation. This high efficiency is achieved by the two-in-one solution with the drum coater and the fluidised-bed dryer. The changeover takes place within minutes via an assembly and storage rack. Powerful air, measurement and control technology is also integrated in the housing of the laboratory unit and can be used by both units. The advantages of using this unit lie in its high flexibility, as a large batch range is covered.

A big plus in flexibility is added by the wide range of integration options of other systems. The P 1-6 pharmaceutical mixer is the perfect complement for mixing processes. By simply exchanging the mixing by the spheronizer bowl, pellets can be produced in no time at all. With flexible systems, it is possible to switch between different technologies at a relatively early stage of development.

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One size larger is the MidiLab RC, a mobile, highly flexible unit with a likewise extremely wide range of applications. Both the fluid bed and tablet coating module can be used. While the coating module allows film and sugar coating in three different drum sizes, the fluid bed module offers drying, top and tangential spray as well as Wurster coating in four different material bowls. Here again, the modules can be changed without tools.

MidiLab RC with fluid bed module

Flexible in the **choice of technology**

In the laboratory or pilot plants, the respective process can also be evaluated, i.e. whether, for example, a top or a tangential spray process should rather be used. A decisive step: after all, any change to the existing spray technology in the pharmaceutical industry must later be recorded by a revalidation and requalification process, which can sometimes be very time-consuming depending on the content of the master batch manufacturing protocol. Therefore, it is even more important that certain procedures can be established before the actual manufacturing process in the laboratory or pilot phase.

In order to show the challenges and the influencing parameters when changing the process, it is worth taking a closer look at the granulation process, here the example of the top/tangential spray process in fluidized bed drying. Here, the powder particles are fluidized. The liquid or binder solution is finely sprayed so that bridges are built between the powder particles. There are therefore enough parameters that influence the process. This includes, for example, the air inlet temperature. The higher this is, the finer the granulate. And vice versa, a larger granulate results. Increased humidity also causes larger granules, but also longer drying times.

The position of the spray nozzle is also important. If the nozzle is too close to the fluidized bed, coarser granules are obtained. If the position is too high, the binder will be dried before it reaches the powder particles (spray drying effect) and finer agglomerates will be produced.

Minilab RC with fluid bed dryer filter and topspray nozzle

These few examples already show that many parameters determine the success of a granulation process. It is therefore all the more important to know these precisely and to master them with flexible plant concepts already in the laboratory and pilot phase.

Flexibility in production

And a trend towards flexible lines has also been observed in production systems in recent years. Increasingly smaller batches are required and at shorter intervals. The throughput often fluctuates. For the customer, this means that his system should be just as flexible and adapt to the respective circumstances, be it in terms of the ingredients or the batch size. Depending on the size, the Diosna CGS concept is designed for batches from 25 to 600 kg and can be equipped with different feeding and discharging solutions. Another advantage is the filling quantities, which can cover between 30% - 90% and thus cover a very large batch range. A construction design of the production plants, which allows the retrofitting of further technologies (spray nozzles, measuring technology, etc..), also increases the level of flexibility. „Users can map different granulation and drying processes with the system and thus react quickly to market requirements“, says technologist Andre Duwendag. Depending on the containment requirements, the systems can be expanded to process highly active substances.

Conclusion: Flexibility in granulating is possible today. However, fast batch or even process changes only work with a sensible scale-up concept and a machine design focused on flexibility. Diosna not only provides a good basis for this with the design of its systems and equipment, but also has enough experience to assess how individual parameters influence the process and thus also the product properties.

Several steps to the **perfect granules**

Regardless of which substances are ultimately to be granulated, the granulation process involves some or all of the following steps:

- Mixing of the ingredients
- Spraying of the granulating agent to distribute the liquid in the mixture.
- Granulation phase, in which the bridges between the individual particles are built up. These are then compacted until the typical snowball structure, i.e. the granulate, is formed.
- Discharge and continuation to the drying or sieving process.

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About us

DIOSNA - Qualität Made in Germany

Everything under one roof: DIOSNA's machine engineering and technology offers everything from compact systems for small-scale operations to fully automated solutions for large-scale operations. The product portfolio offers mixers, granulators, dryers and coating systems for the pharmaceutical and cosmetics industries. It also provides a wide range of products for the food industry including the most important dough production processes from dosing, pre-dough preparation and kneading to transfer logistics - for research, pilot and industrial production.

Joint product development with the customer, process planning as well as optimisation, efficient project management and comprehensive after-sales and value-added services are continuously optimised and customer-centred yesterday, today and tomorrow.

This is why DIOSNA customers have appreciated our quality, performance, competence and philosophy for over 135 years.

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About the autor: Andre Duwendag is a pharmaceutical technology specialist at DIOSNA Dierks & Söhne GmbH. He began his career at DIOSNA after successfully completing his studies in process engineering with a Bachelor of Science degree at Osnabrück University of Applied Sciences in 2014. In the DIOlab in Osnabrück, he is mainly responsible for customer trials, test runs of various kinds as well as technological consulting and further development of existing and new products for the pharmaceutical industry.

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