Scale-up in granulation

Successful change over from laboratory to **production scale**

A scale-up can be compared to a weather forecast. It is usually correct for the next two days, but the forecast for the next week becomes increasingly imprecise due to the many influencing parameters. The same applies to development processes in granulation. However, with a careful scale-up, the scale-up succeeds.

Scale-ups are by far not only interesting for the development of new formulations. Often, it is a question of improving a product, optimizing an existing process or addressing the issue of energy efficiency. A few examples will show how a well thought-out scale-up can improve product development and thus shorten the time to market.

Raw materials of the same type do not always have **identical properties**

A validated process with high-shear granulators was no longer working as required, even though nothing had been changed about the process. Moisture, temperature, bulk densities, and other parameters had remained the same. However, there had been a change in supplier, and one of the raw materials was being sourced from a new manufacturer.
Investigations at the DIOSNA Test Center revealed that this raw material displayed a different capacity to absorb moisture. Based on this insight, the Froude number was increased – initially in the laboratory – and the granulating fluid was adapted, and after this the process delivered the required product quality again. It was extremely important for the customer that the changes were minimal and that no new validation process was necessary.

Faster **time-to-market**

A customer wanted to improve the quality of their product and decided to switch from a low-shear mixing process to a high-shear one in order to do this. However, this meant that the process needed to be revalidated quickly. The models for this were developed successfully by DIOSNA within the space of a week with two scale-ups. As a result, the path was clear to transfer the results via the scale-up from the preliminary tests straight into production with the active ingredient. And this meant that validatable results were available within an extremely short period of time. Furthermore, the customer did not only benefit from the fast revalidation process, but the quality of the product was also improved.

Adaption of the **granulation process**

In another project, the aim was to optimize the manufacturing process. In the laboratory, therefore, a process change was initially investigated on a small scale. The new optimum parameters were determined on the basis of several small batches. The process was then switched from the previous top-driven to a bottom-driven granulator from Diosna. Now less granulation liquid had to be used to achieve an identical target particle size. As a result, the overall process time was shortened and significant energy savings were achieved.

Paying attention to product- and process parameters

So how do you assess the success of a granulation process? It should be fast, robust, reproducible, and controlled – and it should also always deliver the best possible yield. But while this can be easy to do in the laboratory, it is often much less straightforward at the production stage.

In addition, many operators fail to achieve their full capabilities during scale-ups because they do not pay enough attention to the product and process parameters. Inaccuracies often creep in during scale-up, the impact of which is not felt until later on in production. An imprecise scale-up will always have a knock-on effect in terms of subsequent product quality.

Key parameters in the **process**

Many parameters play a role in deciding on the success and quality of the resulting product. These include, among other things, properties of the raw materials such as particle size, structure, density, solubility, or stability. But there are also a number of factors that can be tweaked in the process itself. For example, the particle size of the granules is defined by the method by which the granulation liquid is added (manual addition or spraying with nozzle) and by its infeed rate.

The mean granulate size depends on the specific surface area of the additives, the moisture content, and the level of saturation of the agglomerate with fluid. The moisture content is also an essential parameter, as problems can occur during the granulation process – such as adhesion to the inner wall of the mixing bowl. In addition, the filling rate and speed of the mixing tool and the chopper also play an important role.

Important rules for scaling up

Regardless of the process step, there is one golden rule that always applies during a scale-up: whether the process in question is high-shear granulation, a single-pot process or fluidized-bed granulation, the increase in the size of a line or process when upscaling should never exceed a factor of 10. If the increase in scale exceeds this factor then the uncertainties will grow.

Looking specifically at high-shear granulation, mixers with a volume ranging from 0.25 l to 10 liters have proved successful for product development in the laboratory. So, if a 6-liter bowl is chosen for development, a maximum volume of 60 liters is then chosen for the scale-up, for example for the production of clinical samples. Production can then start with up to 600-liter capacity.

In addition to consistent quality of the raw materials, reproducible conditions must also be ensured for production – i.e. room humidity, room temperature etc. Over the period of several decades. DIOSNA has developed numerous scale-up models that incorporate many other parameters. These are repeatedly re-tested and adjusted in investigations and trials.

When are **processes 'similar'?**

What else needs to be taken into account? As a general rule, two processes are deemed to be 'similar' if there is a geometric, kinematic, and dynamic similarity between them.

In terms of 'geometric similarity' the key factors include e.g. the ratio between the height and diameter of the bowl or the ratio between the cylindrical and conical part of the mixer.

The term 'kinematic similarity' refers to the similarity of the ratio of speeds between two measuring points. The rotational speed is not the key factor here, but instead the circumferential speed at the outer ends of the mixing tool (which is known as the 'tip speed'). Here, the faster the mixing tool, the higher the tip speed – which is typically at a maximum of 7 m/s – and the higher the energy input, resulting in larger granules.

The 'dynamic similarity' relates to the ratio between forces at two measuring points. In order to describe dynamic processes, it is important to look at dimensionless parameters like the Froude number and the Reynolds number. For scale-up purposes the Froude number in particular has proved to be very useful. It is an expression of the interplay between the centrifugal force and the centripetal force. Here, the centripetal force is generated by the wall (creation of a 'compaction zone'), whereas the centrifugal force presses the particles against the wall of the mixer. In order to achieve comparable granulation results between the individual scale-up steps, the dimensionless Froude number should always be kept the same. But watch out – the larger the mixer size, the smaller the Froude number which can be reached. Mixers at laboratory scale have motors that are more powerful relative to their size. Here, higher shear loads and intensity of agglomeration are attained because higher impeller speeds (i.e. Froude number) can be achieved. It follows from this that the maximum rotational speed of laboratory mixers should not be chosen too high.

Modular systems for easier **scale-ups**

Particularly successful scale-up results can be achieved with flexible, modular systems with exchangeable bowls that can cover the different process steps – such as mixing, granulating, drying, and coating.
A good example here is the Laboratory Mixer P1-6 from DIOSNA, which is a great starter system for scale-ups. All sizes of DIOSNA bowls right up to production scale offer geometric similarity, and the bowls, which can be exchanged without the need for tools, start from a capacity of 0.25 l and are therefore also available for small scales (20 g of powder mixture).

In addition, robust touch-screens, containment options or the ability to connect automatic loading/emptying systems, air conditioning and the ability to run the process with solvents are all available. This makes it much easier to transition from laboratory scale to pilot or production scale. One aspect that is at least as decisive for a successful scale-up and for subsequent validation of the processes is meticulous logging of the processes and parameters. This is where our 21 CFR Part 11-compliant software packages come in, offering historic data storage with audit trails and batch reporting.

Among other things, DIOSNA offers PAT software packages here with more far-reaching analytical tools for statistical data. The software has been programmed and validared by DIOSNA in accordance with the GAMP guidelines. Alarms can be assigned to all measured values and calculated values to respond if target values are exceeded/fallen short of, and these values can be graphically represented as curves in the batch report. From the measured values the validated program calculates a range of data and key indicators that are interesting both for developers and for production. These can also be used in batch reports, for data backup or for remote assistance.

Conclusion

A well thought-out scale-up lays the foundation for successful formulation and process development. Surprises in production can thus be avoided or at least reduced to a minimum.

About DIOSNA - **Quality Made in Germany**

Machinery and technology from DIOSNA are used all around the world in the processing and production of solids for the pharmaceutical, food and cosmetics industries. The production portfolio includes mixer, dryers and coating systems, fermentation systems and kneading machines for the production at research, pilot and industrial scale.

Product developtment together with the customer, process planning and optimization, project management, aftersales and value added services are continuously optimized with total focus on the customer – yesterday, today and tomorrow.

For over 135 years, customers of DIOSNA have enjoyed and appreciated a philisophy that delivers outstanding quality, performance and competence.

DIOSNA Dierks & Söhne GmbH
Am Tie 23, 49086 Osnabrück, Germany
+49 541 33104-0, info@diosna.de , www.diosna.com

DIOSNA

Author: Michael Benjamin, Head of Technology, Diosna Dierks & Söhne

About the author: Michael Benjamin works as Head of Technology at DIOSNA Diersk & Söhne GmbH in Osnabrück. Michael Benjamin completed an apprenticeship as a Pharmaceutical Production Technician and got studies in Life Science Technologies (graduate as B.Sc. in pharmaceutical technology) at the Technical University of Ostwestfalen-Lippe. After having worked in several R&D positions in the pharmaceutical insdutry he has been with DIOSNA Dierks & Söhne GmbH in Osnabrück since 2016. There, he is responsible for the DIOSNA technology centers and laboratories and for technological development & consulting.