How do you **produce the perfect particle**

Validated processes in granulation

DIOSNA

To produce granules with the desired properties, it is crucial to consider the process parameters but also the scale-up. After all the path of a drug from the laboratory to production entails many surprises. Especially with particles for inhalers, the mixing process plays a decisive role.

Geometric, kinematic and dynamic similarity

Transferred to high-shear mixers, this means: For the product development in the laboratory, mixers with a volume of 0,25 to 10-litres have proven their worth. If for example, a 6-litre container is chosen, a 60-litre volume is selected for scale-up, such as to produce clinical samples. For the production scale the appropriate process parameters for up to 600 litres process volume can then be precalculated.

But the bowl size is not the only parameter, that is important in the scale-up. In general, processes are comparable if they are geometrically, kinematically, and dynamically similar:

- In the case of **geometric similarity**, for example, the **ratio of the height and diameter of the container** is decisive.

- The **kinematic similarity** describes the same ratio of velocities between two measuring points. In this case, **not only the speed (rpm)** of mixing tools is decisive, but the movement speed and circumferential **speed of the mixed material on the outer ends of the mixing tool (Tip Speed)**. The higher the speed of movement of the mixed material, the larger the granules produced tend to be.

- **Dynamic similarity** refers to the ratio of forces at two measuring points. To describe dynamic processes, it is important to look at the dimensionless key figures, in the case of high-shear mixers this is the **Froude number**:

  Fr = n^2 x d/g (n: impeller speed (rotations/sec.) / **d**: impeller diameter (m) / **g**: gravitational constant (9,81m/s^2)**)**

Describing dynamic processes

with the Froude number

When scaling-up mixers, the Froude number has proven to be very useful. It is expressing the interaction of centrifugal force (which pushes the particles against the wall) and centripetal generated by the wall (creating a “compression area”). This includes the speed of the mixing tool (rotations per second), the diameter of the mixing tool (m) and the constant of gravitation (9,81m/s^2). For comparable granulation results between the individual scale-up steps, the Froude number should be kept the same. It is important to know: The larger the mixer size the smaller is the Froude number, which can be reached.

$$\text{Froude \#} \quad Fr = n^2 \times d/g$$

n: impeller speed (rotations/sec.)
d: impeller diameter (m)
g: gravitational constant (9,81m/s^2)

Software packages with **advanced analysis tools**

However, many other parameters flow into the model development. DIOSNA has developed numerous models for scale-up over decades. These are repeatedly checked and adapted through studies and trials. In addition, DIOSNA offers, among other things, a so-called PAT package for the detailed recording of many parameters.

In this case the active power of the mixer engine comes into play, which is measured with a special power meter. The speed of the mixing tool is controlled and measured by means of a shaft via proximity switches and pulse counters.

The following values/key figures are calculated from the measured values:

- Circumferential speed
- Froude number
- Active power minus idle power
- Total energy input of the batch by the mixing tool
- Mixing tool torque
- First derivative of the power curve with indication of the inflection point of the curve

The values are displayed and recorded (selection by the operator). The power/torque values can be assigned with warnings/alarms when adjustable setpoints are exceeded and used as trigger points in the mixer recipe.

When is the **end point reached?**

Furthermore, end point determination is a valuable tool, which is often underestimated. Admittedly, there is no universally valid definition of how the granule should look like at the end of the wet granulation. But a good flowability, compressibility and the desired dissolution profile are crucial aspects. The right selection of the end point should be based on consideration of the entire process and aim towards repeatable results. At the same time, the effects on the subsequent drying, grinding, pressing, and coating processes must be considered.

The granulation end point can be defined by the formulator as the target particle size average or as target particle size distribution. It has been shown that once the desired end point is reached, the granule properties and subsequent tablet properties are very similar, regardless of granulation process factors, such as impeller speed or chopper speed or binder addition.

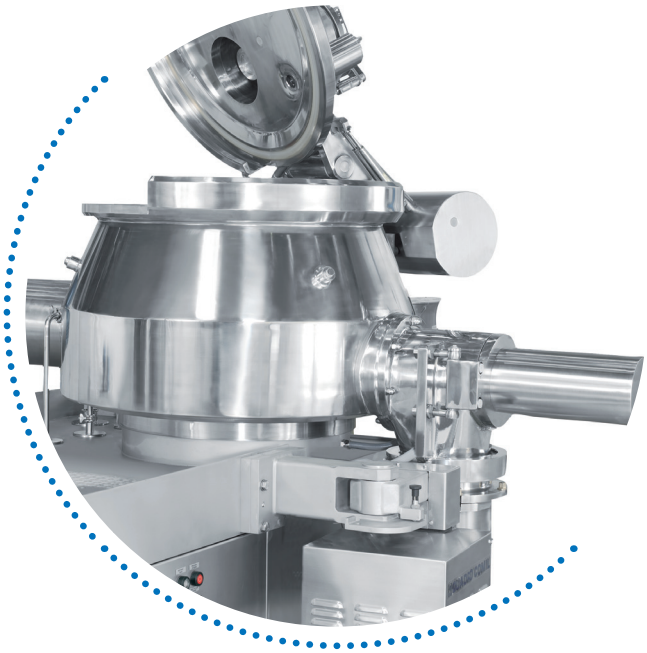
Very often, power consumption and torque are used to determine the end time. This allows a precise determination of the perfect time for the end of the granulation process. This can be read directly on the user interface of the system. Another possibility is the inline particle measurement.

Good practices: **inhalable active ingredients**

The production of active ingredients for DPIs (Dry Powder Inhalers) - powder inhalers used for indications such as chronic obstructive pulmonary disease (COPD) or asthma - is complex. Therefore, the mixing process plays a crucial role. Challenging unlike to other dosage forms: The inhaled active ingredient passes the mucous membranes of the mouth and nose, via the trachea to the area of the alveoli. The absorption area of the lungs is about 70 m^2 and noteworthy, thus much larger than that the small intestine. However, the lungs are designed by nature to deny particles access. Nevertheless, when the particles reach the peripheral area of the lung, absorption of the active ingredient is very efficient. This is why the optimal particle size is so crucial.
The dosage form for DPIs contains two components: an active ingredient and a carrier (e.g. lactose Lactohale 200). The active ingredient particles are much smaller than the carrier particles because the active ingredient particles attach to their large surface area. The optimal particle size is <10 µm. The administration occurs via an inhaler.

Perfect particle properties **enable high efficiency**

The advantages of this dosage form are mainly traceable to the stability of product and formulation (at room temperature or even above). It also offers the possibility of a very low or high amount of the drug release per dose (per „puff“). There is also very low susceptibility to microbial growth. In addition, this method of delivery form is possible for both soluble and insoluble pharmaceuticals. Disadvantages are, on the one hand, that the very fine powder particles tend to stick together. This can impact the drug delivery to the lungs. On the other hand, the inhaler and the cost of production can be associated with higher costs.



Unlike other dosage forms: DPIs are only produced via extended mixing times and high rotation speeds, but without binder fluids. It therefore depends on the adsorption of the active ingredient on the surface of the carrier. This leads to higher adhesive forces between the active ingredient and the carrier. Furthermore, the cohesive forces between the particles of the individual substances are overcome. The recommendation is a „sandwich“ process, i.e. carrier-API-carrier in the mixing stages. Each producing company has its own method for processing this pharmaceutical form. These vary in speed, mixing times, supplementary cooling, etc. Due to the long mixing time which is usually around 10-30 minutes, the material can heat up.

To counteract this process a double jacket bowl is recommended for cooling. DIOSNA mixers are ideally suited to produce inhalants regardless of which equipment and process parameters are chosen. The many years since customers have been using them for production as well as customer’s feedback confirm this. DIOSNA’s technological center – the DIOlab enables to determine the right process and process parameters for the production of DPIs. In addition to testing the suitable mixer, correct process parameters can be determined.

Conclusion and outlook

In the production of DPIs, it is crucial to start with a structured process, initially on a laboratory scale and then to begin the scale-up in a structured way. Important success factor: If the processes are planned and optimised depending on the product development done together with the customer nothing stands in the way of a successful product launch. This lays an important foundation for achieving high-quality granule and a good yield in the subsequent production, and not only in inhalers.

About us

DIOSNA - Quality 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 a variety of industries: from pharmaceuticals and cosmetics to feed and fine chemicals, as well as solutions for the food sector. It also provides a wide range of solutions for 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.

Author: Andre Duwendag, Process Technologist Pharma, Diosna Dierks & Söhne GmbH

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.

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