The key criteria for process selection

Compass for **granulation processes**

Solid dosage forms: Multi-step process or single-pot process?

DIOSNA

Decision support for selecting the right granulation and drying process, considering various critical material properties, and process requirements.

When manufacturing solid dosage forms, such as wet and dry granules for compression, effervescent granules or (micro) pellets for the pharmaceutical, homeopathic and food supplement industries, there are several criteria that are significant when choosing the right manufacturing process. In addition to the requirements for the quality and quantity of the granules and their individual particles, the specific handling requirements of the respective active ingredients and excipients in terms of toxicity, sensitivity to factors such as light, moisture, heat and oxygen play an essential role. Finally, external factors such as budget requirements, space requirements, the need for flexibility regarding product changes and process options, efficiency (downtimes & process speed) and staff availability are also critical. This white paper compares different process options in the context of these various criteria and is intended to provide a decision-making aid for the right manufacturing process. For this purpose, the following process options will be analysed, based on the topic of granulation:

- High-shear granulator plus fluid-bed processor
- Fluid-bed processor
- Single-pot processor

Either discussed or compared according to the criteria listed::

- Specific handling requirements
- Willingness to invest
- Space requirements
- Flexibility
- Product quality

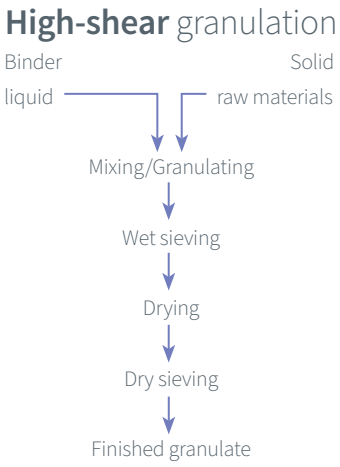
Brief overview of granulation processes

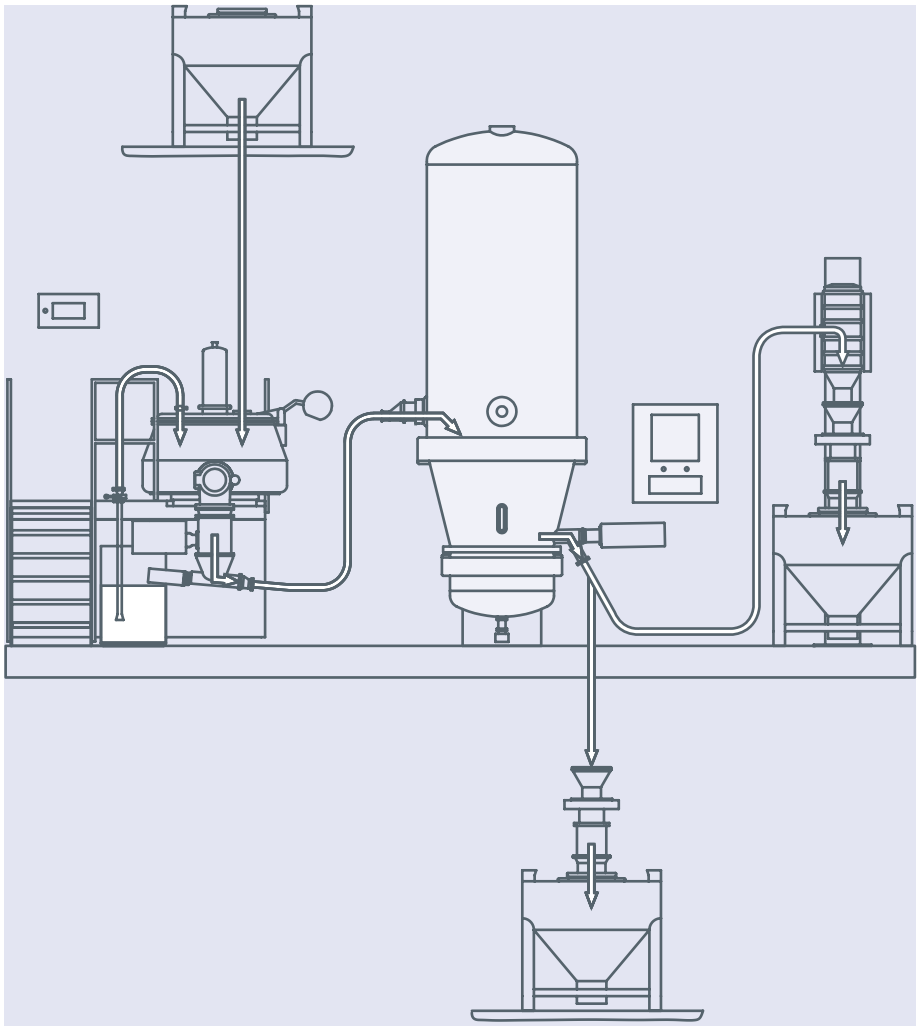
High-shear granulation plus drying

Mixing tool and chopper in an optimised DIOSNA high-shear granulator (HSG) bowl ensure homogeneous mixing and granulation of powdery raw materials. Exceptionally good mixing results can be achieved in just a few seconds and homogeneous moist granulation in ≤ 3 minutes. The moist granulate must then be dried. For example, in a tray dryer (TD) or a fluid-bed processor (FBP).

The quality of the dry granulate in combination with the TD has a higher proportion of fines, in combination with the FBP it is low to medium, the granulate density is in the high to medium (TD) or high range (FBP). The Gaussian curve of the particle size distribution is in the medium range (HSG + FBP) or rather wider (HSG + TD). In terms of particle shape, HSG + TD achieve round to irregular shapes, HSG + FBP rather round shapes.

The compressibility is good. Quantitatively, the yield is exceptionally good. The average product loss in the TD combination is 1-3 %, in the FBP variant 2-3 %. The process time in the HSG + TD combination is ≥ a factor of 4 in comparison to the combination of the significantly more efficient HSG + FBP variant. The absolute investment costs are correspondingly lower in the less efficient variant, but higher in relation to productivity (costs per batch) compared to all other processes discussed. Finally, high-shear mixers can be used for all materials.



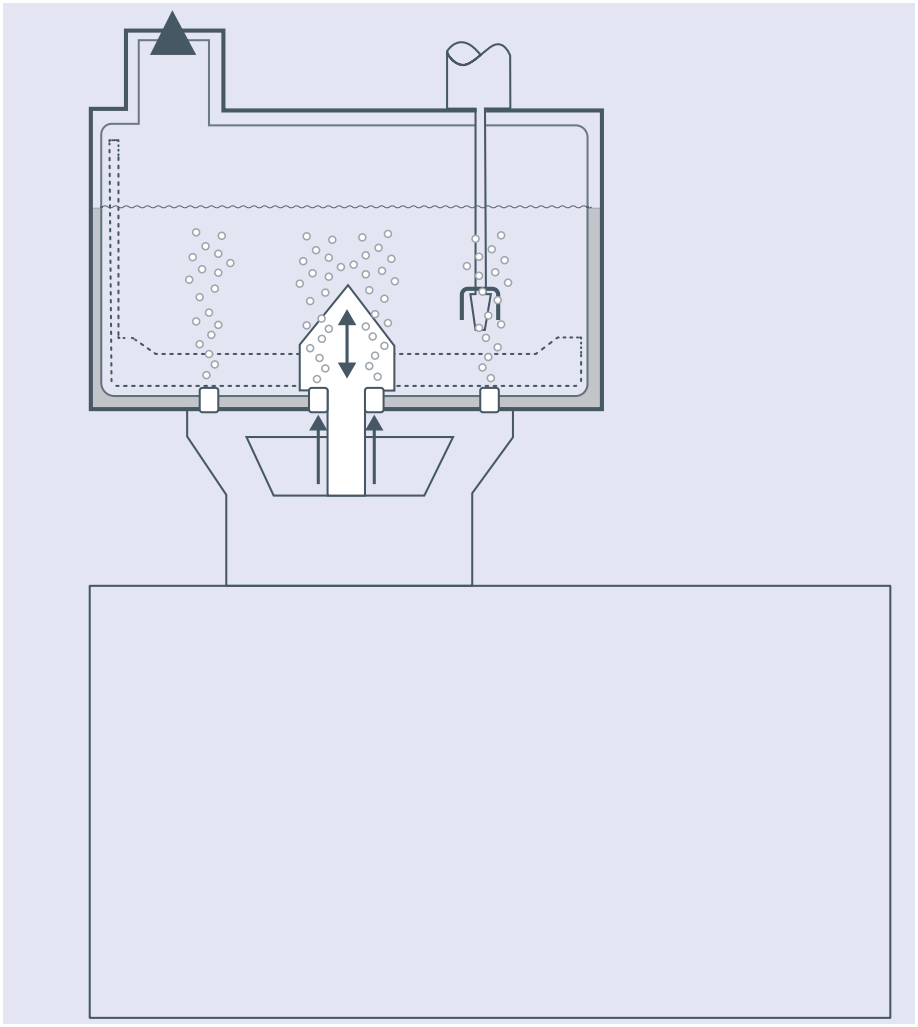


Brief overview of granulation processes

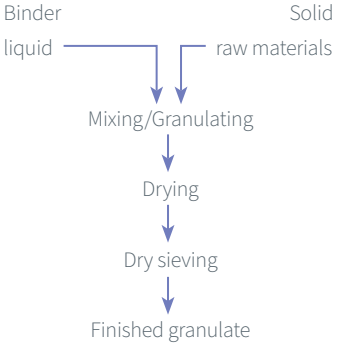
High-shear granulation with carrier gas vacuum drying (single-pot system)

The single-pot system allows mixing, granulation and drying, with drying taking place under vacuum. The vacuum lowers the boiling point, and less energy is required for heating. After the rapid granulation process, drying can be automated. The dry granulate has a medium to high proportion of fines compared to the other methods and the granulate density is high. A medium to wide particle size distribution is achieved, the particle shape is round.

The fines content is in the medium to high range and is due to the sequential drying process. In quantitative terms, the yield of > 99 % is the best in comparison. The absolute and batch-related investment costs are in the medium range compared to the other methods (except for HSG + TD). Virtually all materials can be converted in the single-pot processor and it is particularly suitable for solvent-based processes.



High-shear granulation
with carrier gas vacuum drying



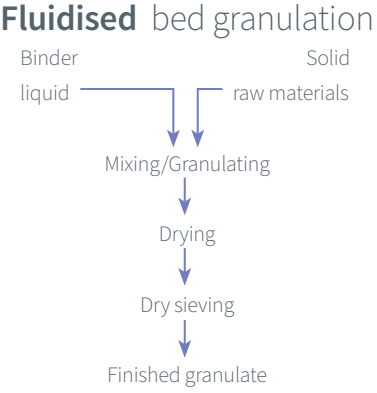
Fluid-bed spray granulation

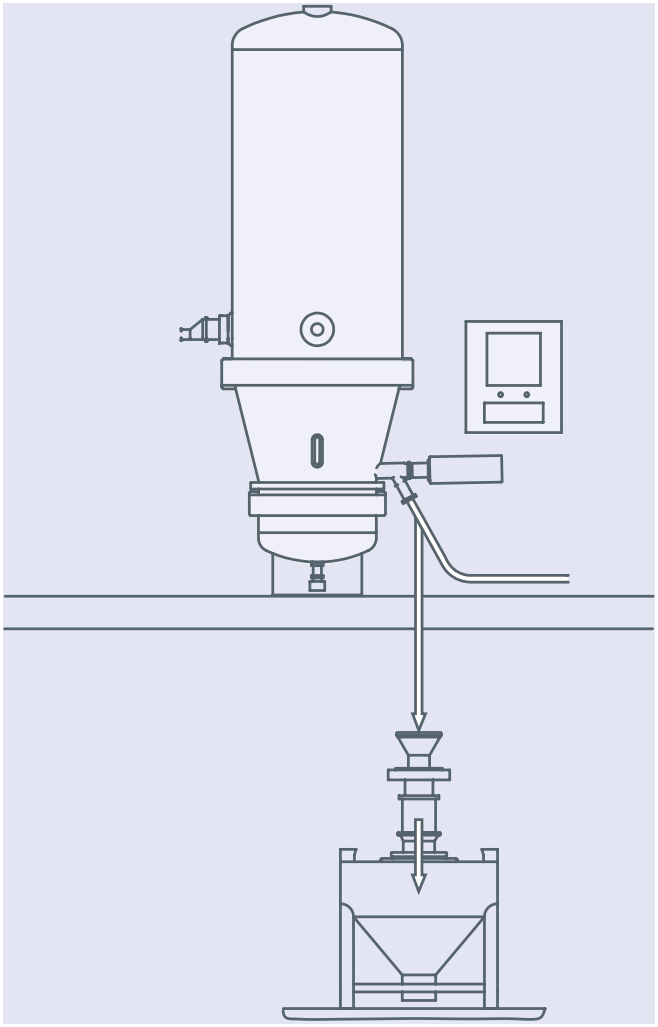
The fluid-bed processor allows mixing, granulation and drying. Granulation takes place without mechanical force by spraying the fluidised product with binders. Compared to the high-shear method, the granulates are more porous and have a raspberry-like structure as well as a reduced particle size and bulk density. The particle size distribution is somewhat more homogeneous and narrower.

The texture leads to improved dispersibility. Granulation can be carried out in two ways. In top-spray granulation, the spray application takes place above the product bed, in counterflow to the drying air. This variant has higher spray drying losses compared to tangential-spray granulation, in which the spray is applied laterally and directly in the product bed near the air distributor.

The spraying time can be reduced by around 30% and the spraying rate increased by around 30%. Despite these and other advantages, the top-spray application is still the most common of the two variants. Regarding the range of applications, it should be noted that fluidised bed granulation is not suitable for voluminous or cohesive base materials.

Fluidised bed granulation





Brief overview of granulation processes

Granule quality of the various granulation processes

in relation to each other

	HSG + tray-drying	HSG + fluid-bed drying	Single-pot processing	Top-spray granulating
Fines content	low	low - medium	medium - high	medium-high
Particle shape	round/irregular	round	round	irregular
Density	high-medium	high	High	low
Particle size distribution	wide	medium	medium - wide	narrow

Specific **handling requieremements**

Active ingredients that are to be added to granules or dosage forms that must have a certain sensitivity for ingestion purposes, require an appropriate manufacturing process. By choosing the right production process, sensitivities to various environmental factors can be compensated for. This refers to temperature, light, moisture, and oxygen.

In addition, the choice of processes is always limited by:

- the process requirements of the raw material properties
- the product target regarding:
  (*particle size, distribution, consistency, compressibility, flow behaviour, density and product yield)*
- toxicity
- product properties
- production environment

There are several specific handling requirements in relation to the processing of active ingredients or excipients, which are discussed below. A good choice for granulating or **drying heat-sensitive materials** is the **fluid-bed processor** or the combination of a **high-shear mixer** and **fluidized bed system**.

The process air is heated or cooled by an air treatment unit before it flows into the processor. During fluidisation, the particles move freely. This supports excellent heat and mass transfer. No „hot spots“ are generated by the pre-tempered air and a uniform temperature distribution is guaranteed. Thermosensitive ingredients are therefore in good hands with this technology. Drying with low supply air temperatures logically only extends the process duration according to the selected parameters.

Single-pot granulation is also suitable. This is because the drying principle influences the boiling temperature of the granulating liquid supplied. This is reduced by the vacuum applied, enabling drying at lower temperatures (Ø ≤ 40°C). Heat is transferred via the container wall. In order to maintain the target temperature in the entire mixing batch, the temperature in the container wall is slightly higher. This may result in „hot spots“ for very sensitive substances.

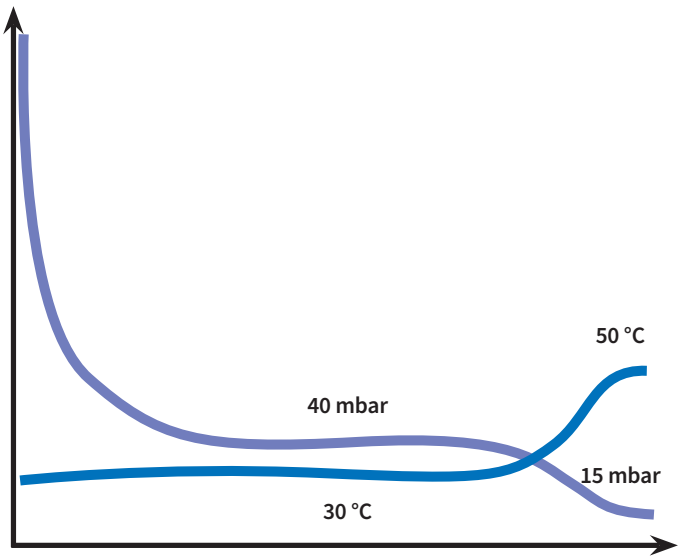


Fig. 3: Exemplary illustration of the drying process in a DIOSNA single-pot processor
The vacuum pressure (mbar) and the temperature of the granulate in the mixing bowl during the drying process are shown. There is an increase in product temperature towards the end of the drying process (decrease in vacuum). The increase in temperature of the granulate results from the absence of moisture, i.e. the achievement of the drying target. Previously, heat was transferred to the moisture present, which was then removed by the vacuum. If the moisture is reduced, the temperature in the mixer increases.

Substances that are **sensitive to oxygen**, **light or moisture** are best handled in a **single-pot processor** if they are to be granulated. The closed process minimises disruptions and product transfer for the purpose of drying the moist granulate can be dispensed with. In the case of **light sensitivity, fluidised bed granulation** is also suitable; the decision on this can be made depending on the desired granulate quality.

The operating principle of the single-pot system explains why it is particularly suitable for processing **oxygen-sensitive materials**. In the single-pot process, the processes of dry mixing, granulation, drying and then sieving are carried out in one system. Contact with the environment, and therefore exposure to oxygen, is greatly reduced compared to the other processes - except for fluidised bed drying. Carrier gas nozzles are located at the bottom of the mixing container, through which inert gas (nitrogen) or dry air is channelled into the granulate and thus transports the moisture to the vacuum pump. This means that you can optionally work without air (oxygen). The points listed also speak in favour of using the single-pot process for **moisture-sensitive substances**. The moisture content of effervescent granulate is generally less . To avoid an effervescent reaction, the raw materials supplied must have an extremely low moisture content. Contact with water would immediately cause an acid-base reaction and the dissolution of the product. The **vacuum granulator** or dryer acts independently of the ambient air humidity and is therefore ideally suited. In addition to dry granulation with a roller press, **high-shear granulation** with subsequent **fluidized bed drying** is also an option. However, this requires several steps to granulate the alkaline and acidic components separately.

Further specific handling requirements are also necessary when dealing with noxious or irritating substances. In order to protect operators or experimenters from them, it may be necessary to work under containment conditions. There are **6 Occupational Exposure Band levels** (OEB levels), which allow toxic substances to be categorised according to their hazard potential, with the assigned OEB value describing the toxicology of the pure substance. The classification according to OEL is also related to this. The **Occupational Exposure Limit** indicates the concentration to which personnel are exposed.

Various containment solutions are available on the market for processing highly active ingredients. These include:

- Safe interface systems
- Isolator solution for R&D
- Single-use options
- Closed systems

A distinction must be made between the solutions depending on the manufacturing scale. Isolators have proven themselves in the R&D sector. This is because, in addition to the convenient and process-flexible handling of high-shear granulators, fluidised bed dryers and mills, a high level of safety and dust-free working is guaranteed. This allows developers to open the equipment at any time, take samples and optimise recipes.

A very good alternative solution for high-frequency containment operation is product production in a single-pot processor. No product transfer is necessary here, and although process optimisation can also be achieved through containment-appropriate sampling, it is also possible to use dust-free process analytical technology (PAT) - as in the isolator.

In addition to feeding, the cleaning method plays an important role. The aim is to achieve dry, clean and dust-free systems that harbour no risk of contamination. To protect the operator, all solids must be bound before the system is opened.

This can be realised very well in both variants just described. Regarding isolator technology, however, it should be noted that all components must be cleaned individually: high-shear granulators, fluidized bed dryers and mills. The single-pot processor simplifies this process many times over, fully automated and quickly.

Closed systems must also be used on the production scale of containment batch production. Fixed connections and vacuum conveying between the granulator and dryer in the system combination or in the single-pot variant.
To summarise, the choice of containment variant depends on this:

1. **Which granule quality is to be achieved?**

2. **At what frequency the application takes place?** (standard or sequential)

3. **Which safety level is to be achieved?**

4. **How much process flexibility is required?**

For sporadic application, single-use is the cheapest and simplest alternative.

Investment

Also, whether in the pharmaceutical, food supplement or chemical industry, the aim of the manufacturing industry must always be economic efficiency. Some critical points are among others:

- High-priced active ingredients & excipients
- High-priced solvents
- Investment costs
- Productivity costs
- Downtimes

In terms of investment costs, it can be said that the method included at the beginning, mixer-granulator + tray dryer, initially has the lowest absolute investment costs. This variant is a good choice for handling inexpensive input materials that require simple handling and a medium level of productivity. There are no containment options here, and the environment and surroundings can influence the processes. Processing is simple and, compared to the other methods, only little space is required in the technical zone.

The investment costs are highest for the combination of high-shear granulator and fluidised bed dryer. On the other hand, the process flexibility is the greatest. So, if you want to use several process options - mixing, wet granulating, drying, granulating, pellet coating - this is the right choice for you, and there are also a variety of options in terms of granule quality, as described above (para. 1) and in Table 1. The flexibility is also reflected in the cleaning process. All individual process units and their surroundings must be cleaned, but this can be done alternately. This applies to non-containment operation.

The DIOSNA single-pot processor offers the highest product yield and even sticky materials can be processed very well thanks to an integrated wall scraper. The impeller is installed at the bottom of the mixing container, and a chopper is also attached vertically from the lid. These three factors lead to very good mixing and granulating results with excellent heat transfer and a particularly high product yield. Ideal for more expensive products. Solvent recovery, such as methanol, can also be easily carried out using a condensate collection container. The flexibility in terms of process changes cannot be compared with the HSG + FBP combination. The quick and easy cleaning makes both processes immediately available. Even after containment applications, which are easier to use here.

Overall, processing in just one system reduces the incidence of errors compared to implementing different process steps in different devices. Fluidized bed granulating offers a similar advantage in this context. In terms of space requirements, it can be said that these are lower in both the technology zone and the production zone. This is because space is only required for one device. In the case of the single-pot system, a lower ceiling height is also required in comparison. The investment costs for the single-pot processor lie between the other two granulator combinations. It requires fewer personnel for operation and cleaning.

Investment-relevant parameters of the different granulating processes in relation to each other (technical requirements)

	HSG + tray-drying	**HSG + fluid-bed drying**	**Single-pot processing**
Investment	very low	high	low
Space requirements GMP	very low	low	very low
Required ceiling height	low	high	medium
Material output/drying time	1 batch/24 h	3 - 6 batches/8 h	2 - 3 batches/8 h
Solvent recovery	expensive	expensive	cheap/simple
Cleaning	2 - 4 h /2 m^2	6 - 8 h/15 - 20 m^2	2 - 3 h/5 - 8 m^2
Climate/Wheather	yes	yes	no

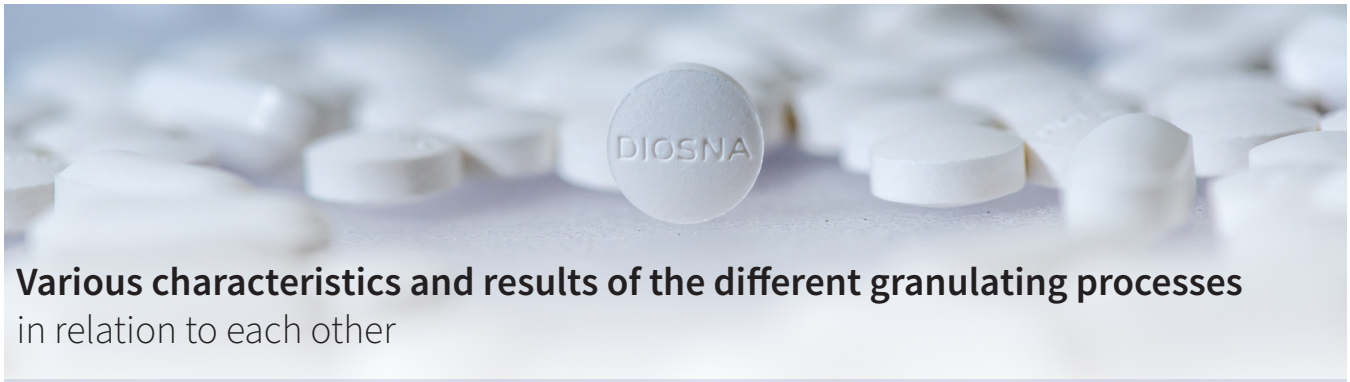
Conclusion

Solid dosage forms are widely used in various industries, such as pharmaceuticals, homeopathy, and food supplements. This includes tablets, effervescent granules, powder granules, and (micro)pellets. Maintaining high quality standards, especially in terms of active ingredient bioavailability, is a constant challenge for the research and manufacturing industries. When choosing a process, several aspects must be considered. Tablets, effervescent granules, or (micro)pellets are often based on wet or dry granules. The characteristics of the target granules are crucial for the desired compressibility, flowability properties, and active ingredient release. The level of protection required for handling materials by operators during processing is determined by the specific handling requirements of the substances. This requires appropriate planning and investment.

Ultimately, the decision will depend on the willingness to invest and the need for efficiency. This white paper compares different granulation processes and their various aspects. The multi-step process, which involves a high-shear granulator and fluidised bed processor, as well as the single-pot process, have been found to be safe, efficient and flexible.

If you require a high degree of flexibility and the use of individual processes, choosing a high-shear granulator and fluidised bed processor is a good option, if enough space is available.

Today, the single-pot process provides a straightforward and secure solution that is not affected by environmental factors and can be easily contained. Dry mixing of highly active substances is also safe for the operator. The cleaning effort is reduced and process-related product transfer is not needed. The process offers high product yield and efficiency, as well as significant space savings. The single-pot processor is a suitable option for producing dry granules, particularly when aiming for high granule density and a medium to wide particle size distribution, despite the potential for high fines content.



Various characteristics and results of the different granulating processes
in relation to each other

	HSG + fluid-bed granulation	Single-pot granulation	Fluid-bed granulation
Automation	automated processes	automated processes	automated processes
Application range	90 % of all materials	90 % of all materials	unsuitable for voluminous and cohesive raw materials
Productivity (incl. cleaning)	high productivity	high productivity	high productivity
Containment	Containment suitable • R&D & pilot scale: in an isolator + (semi-) single-use equipment • Production scale: as a closed system • Feeding and transfer via gravity or vacuum • Containment valves and collection bags • Policing filter • WIP/CIP	Containment excellent • Supplementing the closed system with policing filters, containment valves and single-use equipment • WIP/CIP • Feeding and transfer via gravity or vacuum	Containment suitable • Closed system • Split-butterfly-valve • WIP/CIP • Feeding and transfer via gravity or vacuum
Granule quality	high granule density, medium particle size distribution	high granule density, high fines content, medium to wide particle size distribution	low granule density, narrow particle size distribution
Material loss (cleaning)	0.25 - 1 %	1 - 3 %	0.25 - 1 %
Additional process options	• Dry mixing • Hotmelt granulation • Pellet coating in the fluidised bed system with Wurster-tube possible • Granulation in the fluid-bed	• Dry mixing • Hotmelt granulation	• Top-spray granulation • Bottom-spray granulation • Tangential-spray granulation • Pure drying of moist raw materials • Pellet coating in the fluidised bed system with Wurster-tube possible
Relative investment costs	high	medium	medium

About us

DIOSNA - Quality Made in Germany

All under one roof: DIOSNA machine engineering and technology are used worldwide in the processing and production of solids for the pharmaceutical and food industries. The product portfolio includes mixers, granulators, dryers, coating systems, fermentation systems and kneading machines for research, pilot and industrial production. It also offers a wide range of solutions for the most important processes in dough production, from dosing to pre-dough preparation and kneading through to transfer logistics - for research, pilot and industrial production.
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Product development with the customer, process planning and optimization, project management, after-sales and value added services are continuously optimized yesterday, today and tomorrow with a focus on our customers.

This is why DIOSNA customers have valued quality, performance, expertise and philosophy for over 135 years.

Author: Dr. rer. nat. Jessica Kyereme-Flaspöhler, Marketing, Diosna Dierks & Söhne GmbH

About the Author: Dr. rer. nat. Jessica Kyereme-Flaspöhler, obtained her doctorate from the Faculty of Biology and Biotechnology at Ruhr University Bochum in 2015. She then worked as a marketing product manager in the pharmaceutical industry before joining DIOSNA in 2019 as Head of Marketing. She is currently responsible for the written content of the DIOSNA portfolio.

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