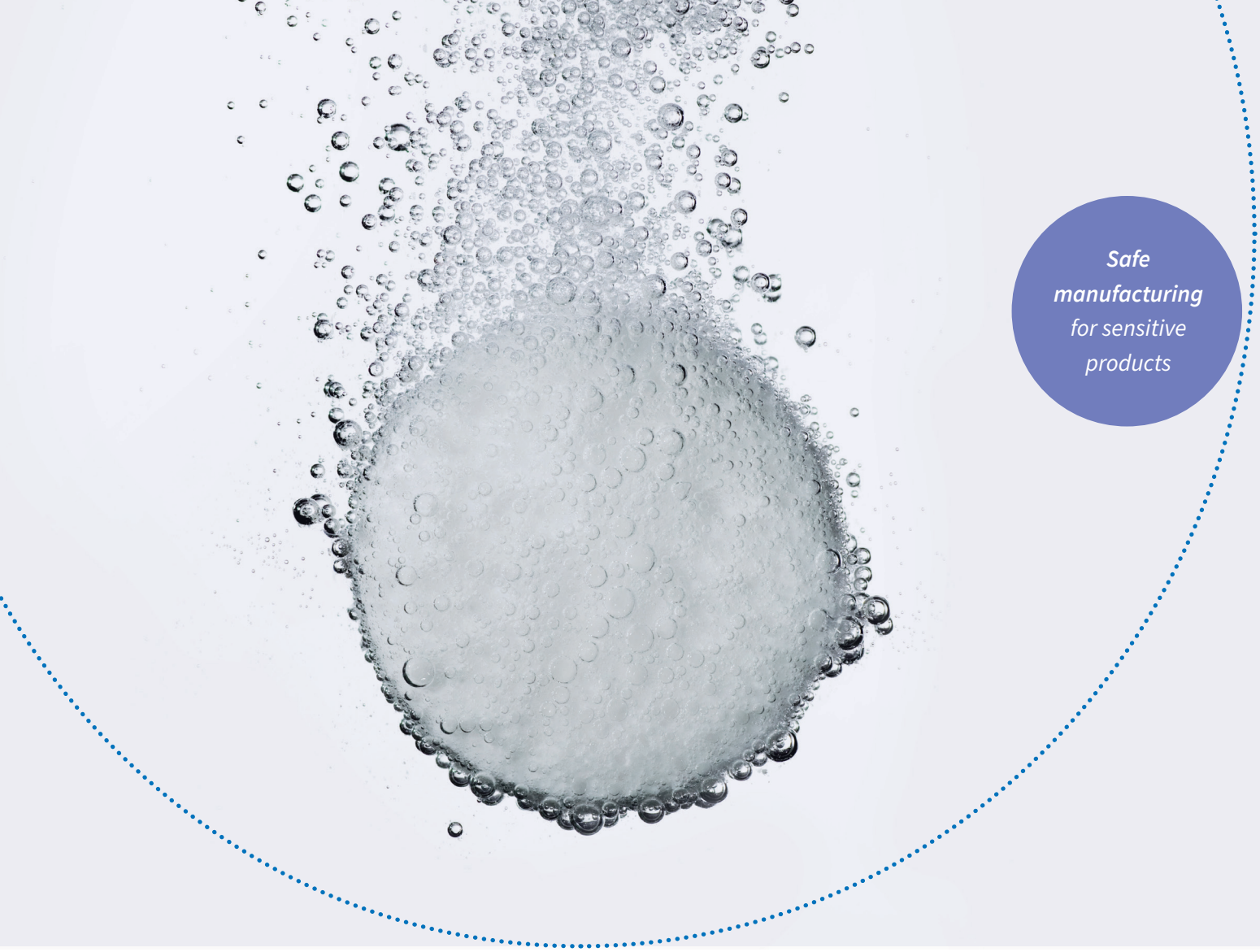


Safe ***manufacturing*** *for sensitive products*

Sensitive **granules**

Minimize environmental exposure by using closed systems

DIOSNA

How to manufacture sensitive products safely: A practical example

Granulation processes are widely used in the pharmaceutical industry to facilitate the dosage of active ingredients in tablets and ensure their even release in the body. The process involves mixing active ingredients with excipients and processing them into granules. This helps to ensure the quality and efficacy of the medication. It is important to follow strict safety protocols during the manufacturing process to prevent contamination and ensure the safety of the end-users. In addition to the desired properties of the particles or granules, the sensitivity of the substances is a crucial factor in determining the appropriate process.

The products listed below require special treatment due to their unique characteristics:

- **Oxygen-sensitive products** (highly active) should be handled with inertization.
- **Temperature-sensitive products** should be dried efficiently but gently.
- **Light-sensitive products** should be exposed to low light.
- **Sticky products** that may require a wall scraper.
- **Toxic products** that require containment.

What process technologies are available for granulation?

Granulation can be achieved through various processes:

1. Dry granulation using roller presses is a cost-effective process with a high product yield. Direct compression is also a simple and low-cost process. However, both processes have limitations as not all types of additives, raw materials, and excipients are suitable for these methods of processing.

2. The high-shear process followed by drying in a fluidized bed processor is the most used technology for producing granules and tablets. This process improves the flow properties, homogeneity, and distribution of active ingredients, making the product ideal for further processing, such as pressing into tablets.

3. The one-pot process involves dry mixing, granulation, drying, and sieving in a single vacuum system.

Practical Example: Production of an Oxygen-Sensitive Product

Effervescent tablets are a typical example of an oxygen-sensitive product. Their ease of ingestion belies the special sensitivity required in their production.

The moisture content of effervescent granules is typically less than 0.1%, making it clear that moisture plays a crucial role in the manufacturing process. As such, contact with water must be kept to an absolute minimum. To initiate the acid-base reaction and achieve dissolution, it is crucial to ensure that the raw materials supplied have an extremely low moisture content. This also affects the compressibility and stability of the product.

When formulating, it is important to consider the solubility of the active ingredient, colorants, sweeteners, and flavorings. The ratio between acidic and alkaline components should be around 0.6. Additionally, the solubility of carbon dioxide in water (90 mg/100 ml water) should be considered. The dissolution duration in 100 ml of water must not exceed 2 minutes.

The following additives are also used:

- **Acidic substances:**
  citric acid, tartaric acid, ascorbic acid, etc.
- **Carbonate:**
  sodium bicarbonate, sodium carbonate, calcium carbonate
- **Binder:**
  PVP K 25 K30 (easily and quickly soluble in water)
- **Lubricants:**
  sodium benzoate, sodium acetate, Carbowax 4000, PEG 6000, etc. (water-soluble)

It is important to maintain a low moisture content for the additives.

Advantages of **One-Pot Technology**

High-shear granulation followed by fluidized bed drying involves several steps. The alkaline and acidic components are granulated separately and then mixed before tabletting. This process requires multiple steps and extends the processing time.

In contrast, one-pot technology allows acidic and alkaline raw materials to be processed together, reducing the number of process steps and saving time. The vacuum drying system and the heating and cooling units significantly impact product quality and process times. One-pot granulation is especially beneficial for processing highly active ingredients, such as effervescent tablets.

The one-pot technology is a gentle production process that allows for fast drying and simple operation. It is a closed system designed for GMP and includes CIP cleaning, ensuring dust-free operation. This makes it ideal for containment applications.

The technology‘s superiority is demonstrated by its ability to operate under vacuum. Under vacuum, the temperature at which the granulation liquid evaporates is greatly reduced, resulting in a significantly shorter drying time. This process fulfils the most important aspect, which is to minimize residual moisture.

The functional principle of one-pot granulation

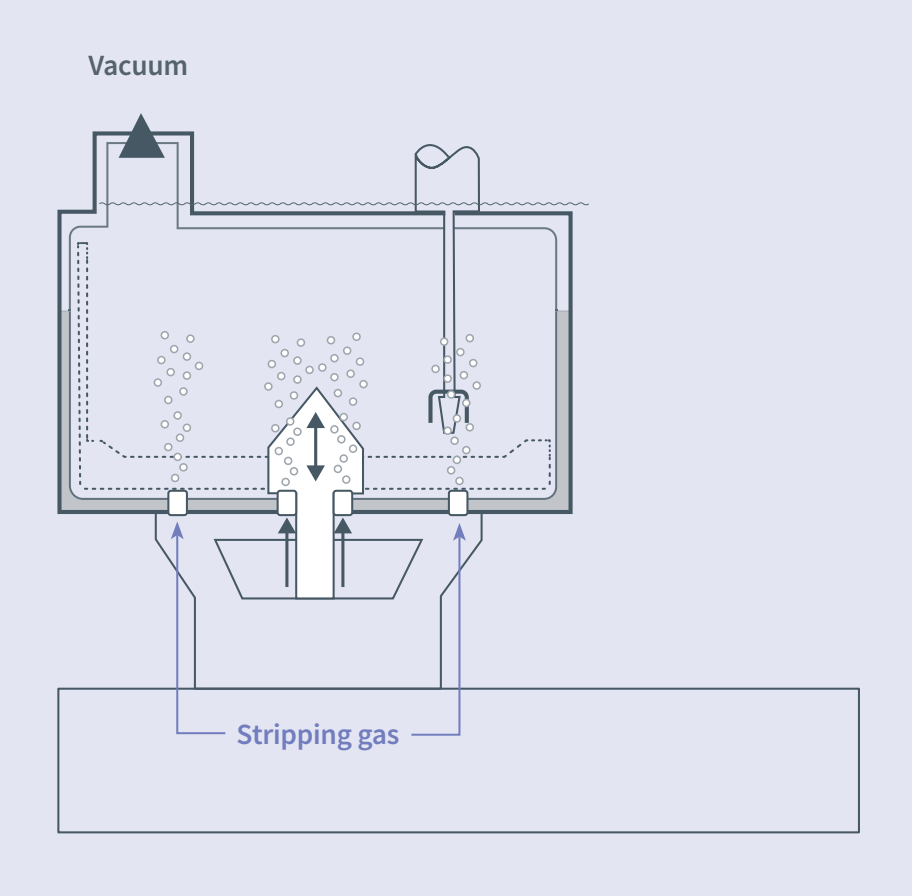
The functional principle of one-pot granulation involves introducing stripping gas (nitrogen) or dry air through installed gas nozzles located at the bottom of the process bowl. This gas flows through the granules and removes moisture from them, which is then transported to the vacuum pump.

The machine used for this purpose is equipped with a cylindrical mixing bowl that has two heating zones and insulation. The mixing tool is mounted with a wall scraper, chopper, and stripping gas floor nozzles. The flap lid is automatically heated to prevent condensation residue.

The vacuum granulator/dryer operates independently of ambient air humidity, allowing it to handle the highly reactive effervescent tablet, which contains acidic components combined with hydrogen carbonates, without causing a reaction.

Recommended application areas

- Ideal for solvent-based products
- Light-sensitive products due to low light exposure
- For high-containment applications
- Expensive products due to high product yield
- Production of moisture-sensitive products
- Ideal for temperature-sensitive products



Drying mechanism diagram

Conclusion

The granulation process is crucial for ensuring the quality and efficacy of medicines. To achieve this, it is important to use manufacturing methods that can reproduce the process reliably, safely, and consistently, especially when processing products that are sensitive to temperature and oxygen or have adhesive or toxic properties.

Generally, there are various granulation processes available, including dry granulation using a roller press or direct compression, which are suitable for oxygen-sensitive products.

However, the most used process is high-shear granulation and fluidized bed drying for granules production. This process requires separate granulation and mixing of components, resulting in multiple process steps with long process times.

Manufacturers can avoid these issues by using the one-pot process, which combines dry mixing, granulation, drying, and sieving in a single system. This process is particularly advantageous for manufacturers of oxygen-sensitive products, such as effervescent tablets, as it allows for gentle, efficient, and fast drying while reducing residual moisture to a minimum under vacuum. The vacuum granulator/dryer operates independently of ambient humidity and prevents the reaction of oxygen-active products.

The one-pot technology offers a viable alternative. It guarantees low-dust or dust-free and gentle development and production, with short process times and easy operation.

The one-pot technology is particularly useful in the production of effervescent tablets, a popular preparation, as it increases efficiency, saves resources, and boosts production output. Overall, the system provides a valuable foundation for the safe development and subsequent production of sensitive products..

Advantages of the one-pot system at a glance:

- Mixing, granulating and vacuum drying in one system
- Easy handling
- Optimum product yield
- Effective and time-saving processes
- Gentle and short drying times
- Dust-free processing
- Gentle product handling
- High flexibility for recipe changes
- Easy cleaning
- Minimal space requirements

FIND YOUR IDEAL SYSTEM!

Checklist

Finding the right system for your company is not easy. Use our checklist to make your free consultation even more effective.

Which system are you currently using?

- ☐ Roller press
- ☐ High-shear granulator + Fluidized bed dryer
- ☐ Single-pot processor

Which product do you process?

- ☐ Processing temperature-sensitive products
- ☐ Inertization of oxygen-sensitive products
- ☐ Processing moisture-sensitive products
- ☐ Processing of light-sensitive products
- ☐ Processing of toxic products

What requirements must the system fulfil?

- ☐ Low-dust (-free) processing
- ☐ Working under containment conditions
- ☐ Inertization to exclude oxygen
- ☐ Mixing, granulating, drying in a closed system

What is the size of your batches?

- ☐ 0,04 – 15 kg
- ☐ 15 - 75 Kg
- ☐ 75 – 190 kg
- ☐ 190 – 600 kg

Which machine filling are you aiming for?

- ☐ <30 %
- ☐ >30 %
- ☐ 50 %
- ☐ 90 %

Which additional equipment are you interested in?

- ☐ Coater
- ☐ Fluidized bed dryer
- ☐ Spheronizer
- ☐ Other: _____

Whataddditional services are you interested in?

- ☐ Carrying out product trials
- ☐ Technological training
- ☐ Technical After Sales Service

Any Questions? We will gladly advise you:
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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.

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