PHARMACEUTICAL SPRAY DRYING

Improve drug properties and production efficiency with spray drying

GEA Engineering for a better world.

GEA.com

Industry-leading technology

Spray drying is a technique preferred by a growing number of pharmaceutical companies to produce better drugs. This ultra-fast and gentle drying technology offers unique possibilities for designing particle characteristics. You can see examples on the following pages.

For nine decades, GEA, through its NIRO® brand, has been a pioneer in all aspects of spray drying and has contracted and installed more than 10,000 plants worldwide. The GEA Test Center is the world's largest and most advanced spray drying technology center. For many years GEA has run a GMP* spray drying facility approved according to European Medicinal Agency (EMA), so GEA's experts are well prepared as partners for you to engineer the required properties into your products.

Traditionally, the pharmaceutical industry has relied on batch production processes. Only recently has continuous processing come into focus as a means of extending production time and ensuring consistent quality. By nature, spray drying is a continuous process and is designed to not only offer high productivity, but also uniform product quality over sustained periods.

*GMP: Good Manufacturing Practice. Guidelines and regulations given by US Food and Drug Administration (FDA), EUDRALEX (EU) or International Conference on Harmonization (ICH).

Powder collection in clean room, custom-designed PHARMA-SD® type PSD-4 at GEA Spray Drying Facility located in Soeborg, Denmark

World-leading expertise

Regardless of the size of your organisation, GEA experts are well prepared to match the services you require. From feasibility testing during initial R&D, to the production of quantities of test material before starting clinical trials, GEA is your partner. When you are ready to purchase your own spray dryer, NIRO® spray dryers are offered with instrumentation and designs that can document reproducible results for later approval procedures. GEA can fulfil your need for a production spray dryer for excipients, Active Pharmaceutical Ingredients (API) or finished drug products with our standard or custom-designed plants.

GEA delivers far more than the stainless steel components that our plants consist of. We help optimize the composition of the liquid feed and the complete spray drying process. During design and project execution, we follow up-to-date quality procedures (ISO 9001:2015 certified) and the GMP spray dryers are delivered with full Factory Acceptance Test (FAT) documentation. Depending on your preferences, we can recommend one of our standard plants, or design a custom plant based on User Requirement Specifications (URS). Customers may choose to manage plant erection and commissioning alone, or with any combination of assistance from GEA. Recognizing GEA as the experts in spray drying, many of our customers ask us to prepare the qualification protocols to follow when the plant is installed. For a Site Acceptance Test (SAT), Installation Qualification (IQ) and Operation Qualification (OQ), GEA project engineers are ready to assist you.

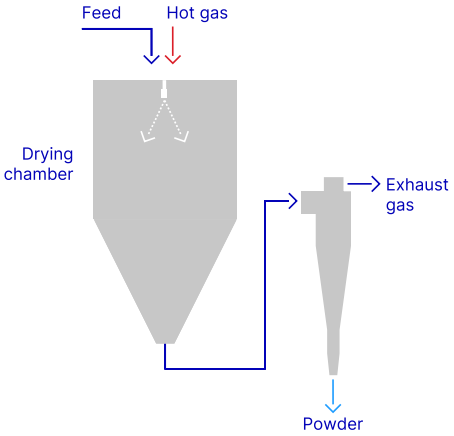
Customers are serviced round the globe by local GEA companies, several of which have their own spray drying specialists.

Drying chamber, HEPA filter and cyclone of standard PHARMA-SD® type PSD-1 spray dryer.

Drying chamber, cyclone and bag filter.

PHARMA-SD® type PSD-2 CC; closed cycle spray dryer.

The spray drying process



As a technique, spray drying consists of three basic stages:

Atomization
A liquid feed stock is “atomized” into droplets by means of a nozzle or rotary atomizer. Nozzles use liquid pressure or compressed gas to atomize the feed while rotary atomizers employ an atomizer wheel rotating at high speed.

Drying and particle formation
Guided by a gas disperser, hot process gas (air or nitrogen) is brought into contact with the atomized feed, initiating evaporation. As the liquid rapidly evaporates from the droplet surface, a solid particle forms and follows the gas flow to the bottom of the drying chamber. The balance between temperature, flow rate and droplet size controls the drying process.

Recovery
The powder is recovered from the exhaust gas using a cyclone or a bag filter. The whole process typically takes no more than a few seconds.

Five ways spray drying can help you commercialize discoveries

1. Increased bioavailability
Many modern therapeutic compounds are stable in a crystalline form but often display poor aqueous solubility, and with this, low dissolution rates. This reduces the bioavailability of the API, sometimes to the point of nullifying the therapeutic effect.

With spray drying, it is possible to co-precipitate an API with a polymer into a stable amorphous solid dispersion (ASD), thereby greatly improving the dissolution rate. The process of dissolving API and polymer in a solvent and then spray-drying the solution is also called spray dried dispersion (SDD).

An interesting technique for improving the dissolution rate is to create nanoparticles that are isolated in larger composite particles and then recovered by the spray drying process. By enhancing the dissolution rate in this way, spray drying has the potential to make treatments possible that are currently unfeasible due to low bioavailability.

2. Modified release and taste masking
Encapsulation offers a number of commercial and medical advantages. It allows the sustained release of, e.g., antibiotics, reducing dosage requirements. By preventing drug concentration peaks, encapsulation is also an effective way to treat chronic illnesses with reduced side effects. Taste masking and the physical protection of the API are other common applications.

Spray drying makes it possible to engineer particles to create specific release patterns and other desired properties. For encapsulation, the API and biodegradable excipients are dissolved and/or suspended. Subsequently, the feed is atomized and dried into a powder.

An interesting alternative approach is spray congealing. Here, the API is melted or mixed with molten excipient and the powder particles produced by atomization and cooling.

3. Aseptic production
Aseptic spray drying offers a number of advantages over traditional methods of aseptic drying like lyophilization. Spray drying provides more control over the drying process and, as a result, over the shape, density and morphology of the final product. Lower running and capital costs also mean reduced overheads.

Production of dry sterile dosage forms often involves mixing the API with one or more excipients. To achieve a homogeneous mixture, the particle size distribution of the excipient(s) must match that of the API. In a one-step operation, spray drying can turn a sterile solution into sterile particles of the required size without any risk of introducing impurities – a well-known problem with milling.

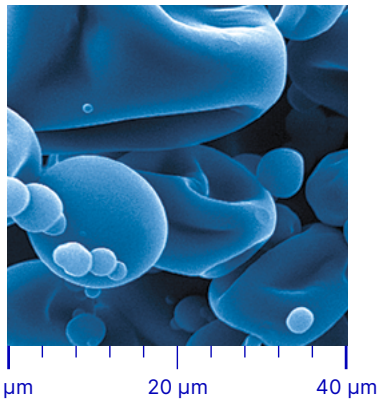
4. Powders for inhalation
The number of medications taken by deeply inhaling them into the lungs is steadily increasing. For pulmonary diseases, this method of administration has long been an obvious choice. However, pulmonary administration is also relevant for other types of drugs, especially large molecules biotherapeutics, such as hormones, peptides and proteins, where tablet administration is challenging due to degradation risks during ingestion and where injection is often unpractical and disliked by many patients.

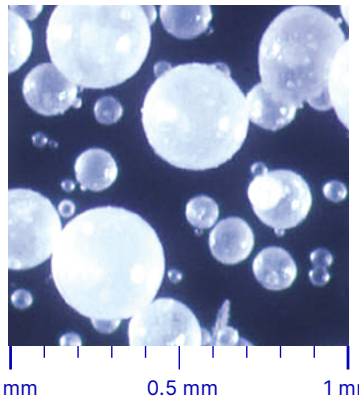
The key to success of pulmonary administration is that the drug is airborne all the way to the target point. Droplets delivered with nebulizers or particles of micronized powders produced by milling, and for example mixed with lactose, have high density. In contrast, lower density powders produced from a multitude of liquid feed mixtures and spray-dried at optimum process conditions can form particles with morphologies especially adapted to inhalation.

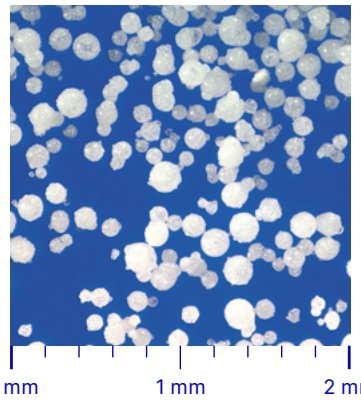
Producing fine particles is relatively easy on small-scale spray dryers, whereas scaling-up while maintaining low particle size can be challenging. For this reason, GEA developed a special NIRO® Two-Fluid Nozzle that gives excellent particle engineering capabilities, even on a large scale, making it possible to accurately control the aerodynamic particle size and powder flow properties – see next page.

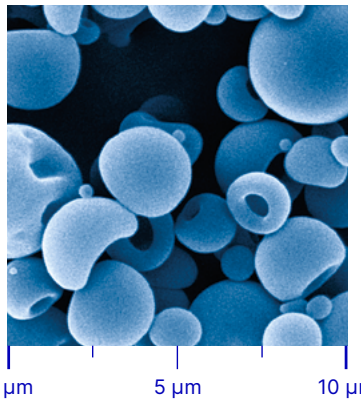
5. Direct compressibility
Solid dosage pharmaceuticals often require a separate granulation step in the production cycle to avoid segregation and to produce a powder with flow properties that can accommodate a high-speed tablet press.

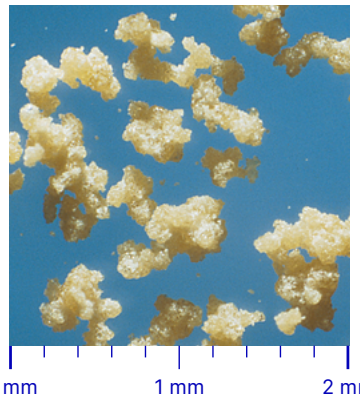
With the Fluidized Spray Dryer – FSD® concept, the granulation step can be made an integral part of the continuous drying process - a technique pioneered by GEA. The FSD® technology can also achieve low residual volatiles content in the final spray-dried powder. The result is a more streamlined, efficient production process and reduced costs.











Five things you might not know about spray drying

The controlled atomization used in spray drying technology offers unique alternatives for drug formulation and particle design.

Rotary atomizer F1.5 X designed to meet cGMP requirements (Patented)

1. **Spray drying is suitable for heat-sensitive materials**
   Spray drying is used for processing heat-sensitive materials on an industrial scale. The thermal energy in the hot process gas is immediately consumed by evaporation, keeping droplet temperatures at a level where no harm is caused to the product.

2. **Spray drying turns liquid into particles within seconds**
   The large surface area of the droplets provides near instantaneous evaporation, making it possible to produce particles with amorphous structure.

3. **Spray drying is relatively easy to replicate on a commercial scale**
   With well over half a century's experience, our process know-how, products and exceptional test facilities put GEA in a unique position to manage the scale-up process.

4. **Spray drying is a robust process**
   Spray drying is a continuous process. Once the set points are established, all critical process parameters are kept constant throughout production and all information is fully traceable.

5. **Spray drying can be effectively validated**
   Quality-by-Design is an integrated way of working for GEA specialists. GEA has extensive experience of supplying NIRO® spray dryers and processes that have been validated and approved by regulators. The precise control of all critical process parameters in spray drying provides a high degree of assurance that the process consistently produces a product that meets set specifications.

Two-fluid nozzle dedicated for large scale GMP production of very fine particles. (Patented)

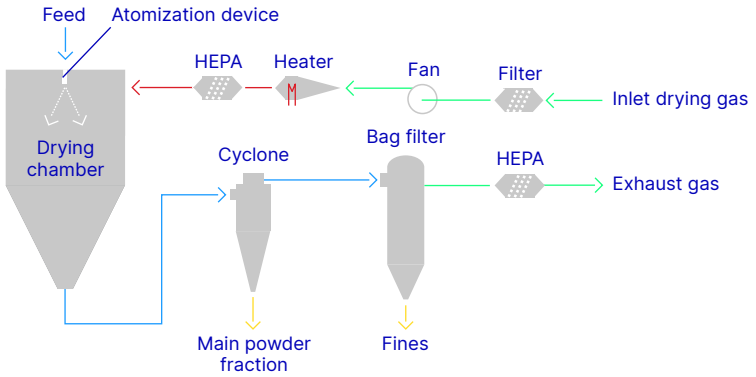
Sanitary two-fluid nozzle facilitates cleaning and ensures reproducible assembly.

We care about your well-being

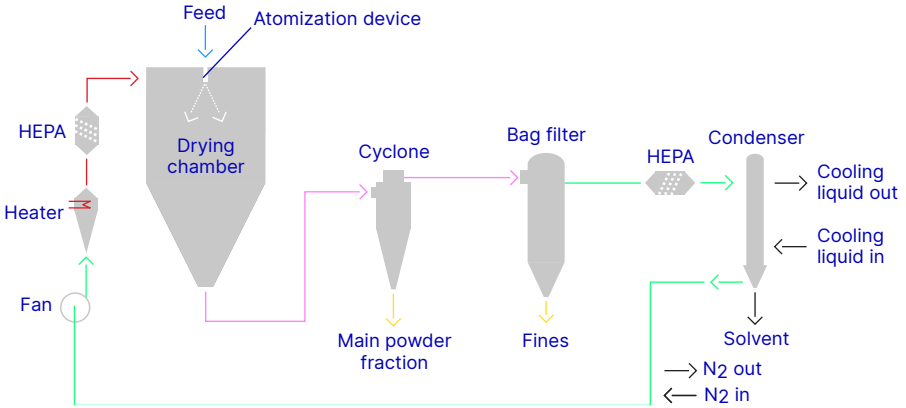
The patient is the ultimate focus of any pharmaceutical company, but safety in medicine manufacturing is of great importance too. That's why every NIRO® spray drying project begins with a risk assessment, incorporating preventative measures at every step of the process.

We eliminate the obvious risk of explosion posed by organic solvent(s) by using nitrogen as a process gas and, in large plants, recycling the gas through a closed-cycle system. Less obvious is the risk of explosion caused by organic powders suspended in atmospheric air and again we may address this risk by using nitrogen. However, depending on the characteristics of the powder, other solutions are available, such as explosion vent panels or automatic explosion suppression systems.

Nitrogen also provides the answer to a third issue: the sensitivity of certain drugs to oxidation, no matter whether the feed stock is solvent or water-based. Although spray drying is a fast, gentle process, some powders require immediate cooling to room temperature. GEA offers different designs for cooling the continuous powder stream.



Once-through configuration



Closed-cycle configuration

Understanding spray dryer capacity

How to characterize the size of a spray dryer

The size of a spray dryer is best described by the flow rate of process gas that the plant is intended to handle. As an example, take 1250 kg/h of process gas. The gas disperser in the top of the drying chamber is designed at this flow rate to supply a uniform and efficient mix of hot gas and the feed droplets produced by the atomizing device (e.g. pressure nozzle).

Similarly, the cyclone design functions to efficiently separate particles from the gas at the 1250 kg/h flow rate. The gas flow also determines the filter area required in the bag filter and the diameter of the ducts.

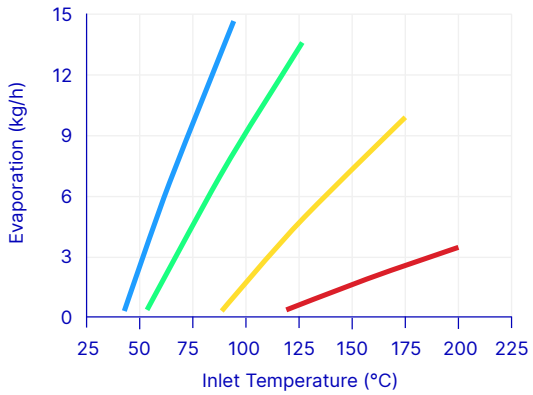
In reality a spray dryer does not “produce” powder but rather it evaporates liquid – to create dry particles. The temperature of the process gas going into the drying chamber is the driving force – and the larger the difference between inlet and outlet temperature, the more energy consumed by evaporation. Water requires more energy to evaporate than for example ethanol. Therefore, the curves on the next page illustrate evaporation rates of four different solvents at an outlet temperature typically used for each solvent.

The evaporation rate and the solids contents in the feed liquid determine the powder production rate. Hence, increasing the solids content in the feed will directly increase the powder rate at the operating conditions.

For a particular size of dryer, such as the PHARMA-SD® type PSD-4, the evaporation curves can be used to evaluate the capacity. If an aqueous feed of 20% solids is dried at inlet/outlet temperatures of 200 °C/90 °C, then approximately 50 kg of water (= 80%) is evaporated per hour and 12.5 kg/h of powder is produced.

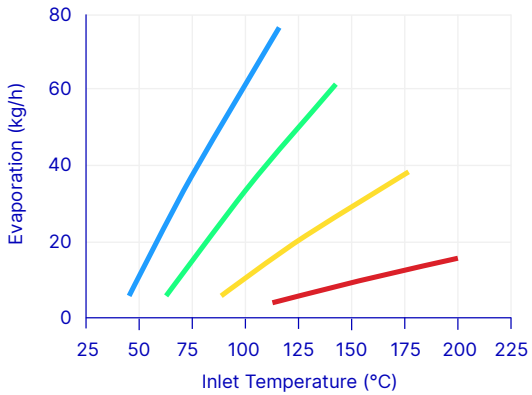
PHARMA-SD® type PSD-1

Nominal drying gas rate: 100 kg/h



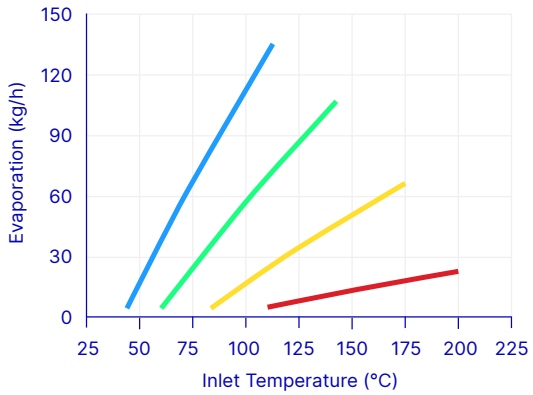
PHARMA-SD® type PSD-2

Nominal drying gas rate: 360 kg/h



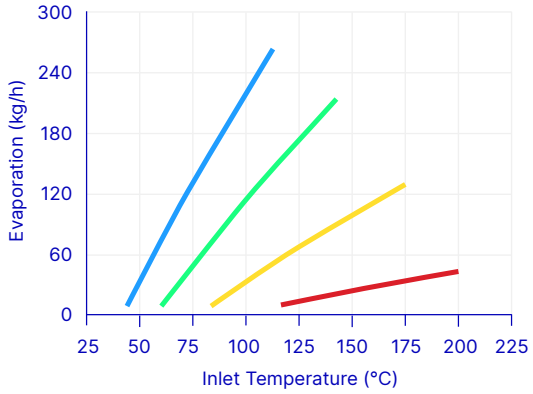
PHARMA-SD® type PSD-3

Nominal drying gas rate: 630 kg/h



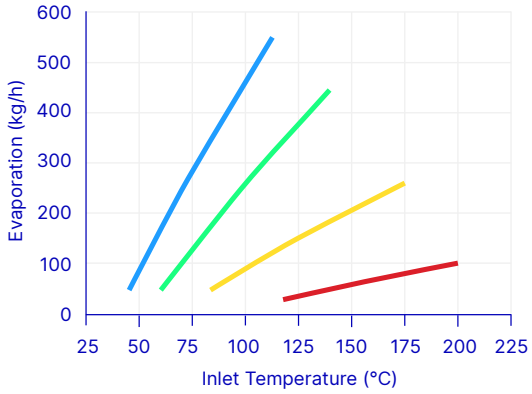
PHARMA-SD® type PSD-4

Nominal drying gas rate: 1250 kg/h



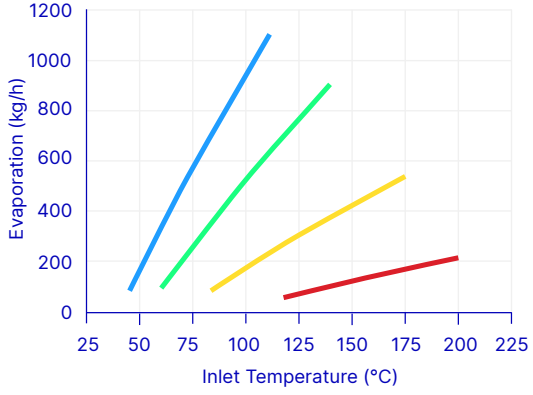
PHARMA-SD® type PSD-5

Nominal drying gas rate: 2500 kg/h



PHARMA-SD® type PSD-6

Nominal drying gas rate: 5000 kg/h

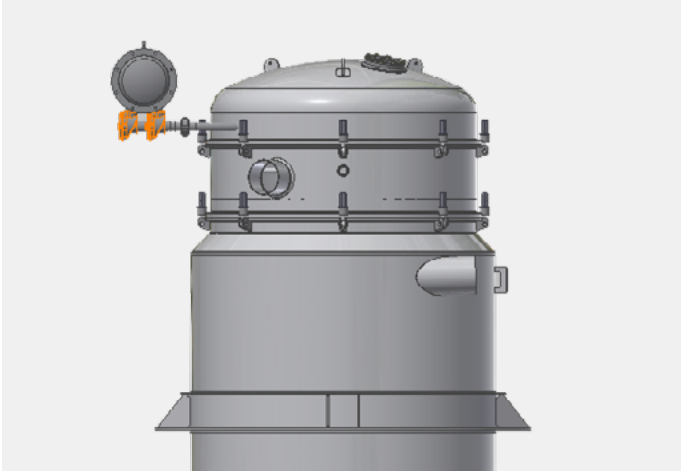


- Methylene Chloride Evaporation Rate at Outlet Gas Temp 40 °C
- Acetone Evaporation Rate at Outlet Gas Temp 50 °C
- Ethanol Evaporation Rate at Outlet Gas Temp 70 °C
- Water Evaporation Rate at Outlet Gas Temp 90 °C

Improving efficiency

GEA's Cyclone Extra Efficiency (CEE) Technology
For efficient and reliable powder separation, a well-designed cyclone is essential to avoid two common problems — smearing due to powder settling in the cyclone, and abrasion.

GEA's latest cyclone solution, Cyclone Extra Efficiency (CEE) technology, helps customers overcome these challenges. The improved cyclone performance provides a higher powder separation efficiency and achieve greater drying economy. The CEE cyclone also greatly improves separation efficiency for small particles, which are traditionally difficult to catch, thus improving powder yields.



Small Sanitary wettable bag filter
Suitable for high potent compounds.

Highly Potent Active Pharmaceutical Ingredients (HPAPI) are an increasing component of today's drug development pipeline driven by more targeted therapies and expanded oncology research. These compounds present safety challenges at all stages of development and manufacturing and require specialized processing with limited release to the production environment.
For this application, the GEA sanitary wettable bag filter is perfect! It allows to ensure that no powder is airborne when the time has come to open the plant for cleaning, thus protecting the operators.

High-frequency, high-speed GEA Motor
For direct driven GEA Rotary Atomizer

High motor efficiency, fast control response, lower motor torque are a few of the advantages of the newly developed high-frequency, high-speed GEA Motor used to drive the atomization wheel.

Cleaning solutions to suit your process

Plant hygiene is one of the first priorities when dealing with healthcare products. GEA offers a full range of cleaning options, with components designed to support specific cleaning methods. The choice of cleaning method has important implications for plant design as well as for control system functionality.

For some products, a hose is sufficient for cleaning the drying chamber while other products require that the atomization device is replaced with an orbital cleaner. Plants dedicated to one product may benefit from an automatic and validated cleaning procedure where cleaning with minimal disassembly calls for special components such as a swing cone access to the drying chamber and automatic CIP (Clean-In-Place) nozzles.

In small spray drying plants like PHARMA-SD® type PSD-1 and PSD-2 ducts and main components are joined by clamp connections, making dismounting and manual cleaning easy. In larger plants with wider ducts, different types of cleaning nozzles can be mounted.

For optimal efficiency, the spray dryer is divided into several cleaning zones and run by a control system with minimal manual operation. Fully automated cleaning sequences can be developed to suit the individual plant and process requirements.

Custom-designed PHARMA-SD® type PSD-4 drying chamber roof with gas disperser and top of bag filter.

The GEA Orbital cleaner cyclone.

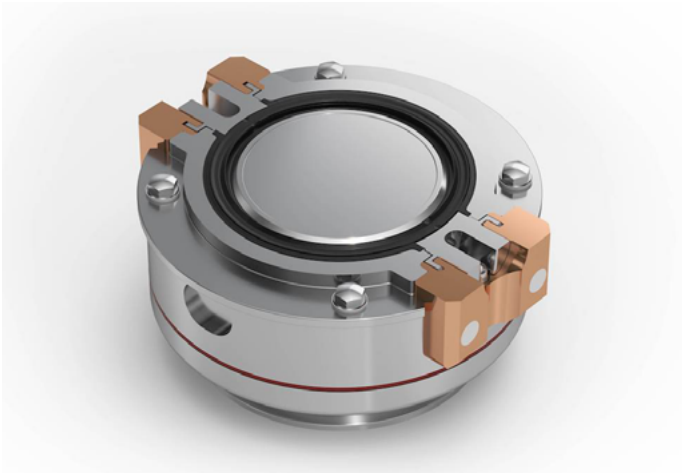
Cleaning requires a swing cone at the bottom of the drying chamber.

Process control, potent drugs and aseptic production

Process control
In GEA's standard PHARMA-SD® plants, the control system is designed for easy operation and display of data following GMP guidelines. Process data and alarms may be logged or transferred/communicated into a distributed control system (DCS). An audit trail is available too. For customized plants with increasing complexity, where recipes are required,or process data are needed for batch reports, GEA offers control systems to match.

Potent drugs
Often HPAPI plants (High Potency Active Pharmaceutical Ingredient) are small in scale and not suited for cleaning. GEA design such plants with solutions for wetting of all surfaces with powder contact. Thus, the risk of releasing powder to the environment is minimized until cleaning is initiated. GEA experts work closely with customers to conduct detailed risk assessments and determine the optimal combination of spray dryer, isolator technology and Standard Operating Procedures.

Aseptic production
Some products must be produced in plants with low bio-burden or even under aseptic conditions. With years of experience delivering such solutions, GEA recently introduced the next generation of ASEPTIC-SD® spray dryers. These plants have an automatic cleaning process involving sterilisation using clean steam. Please contact GEA for more information.



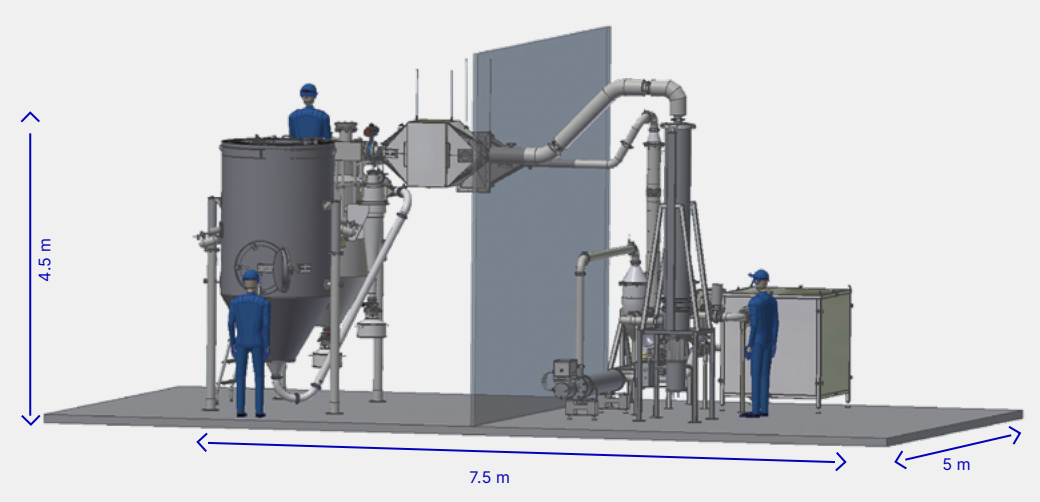
A standard PHARMA-SD® Spray Dryer

A cost-effective path to proven results

Based on years of experience with customers of all types (global pharmaceutical companies, producers of API and finished drugs, and contract manufacture organizations), GEA has developed a proven and robust range of “standard” PHARMA-SD® spray dryers.

Despite the level of customer individuality, in many circumstances GEA’s standard PHARMA-SD® plants are an ideal and cost-effective solution. With no or only minor modifications, the process set-up and the controls software can be configured. This results in significant savings in engineering hours, also when it comes to qualification activities like the Factory Acceptance Test (FAT), Site Acceptance Test (SAT) and Installation/ Operation Qualification (IQ/OQ).

Of course, choosing a standard PHARMA-SD® plant is more than just a financial decision. Your product’s Critical Quality Attributes (CQA) are of paramount importance. GEA’s Test Center provides total assurance, enabling your drug delivery scientists to spray dry and test powder samples before the purchase decision is made. As an experienced supplier to the pharmaceutical industry, GEA welcomes your QA people to audit our quality system and observe how GEA’s qualification protocols and test documentation fulfil required standards.



Standard PHARMA-SD® spray dryer type PSD-2 in closed-cycle configuration.

PHARMA-SD® type PSD-1 spray dryer for closed-cycle operation with solvent-based feeds. Nominal drying gas rate: 100 kg/h.

PHARMA-SD® type PSD-2 spray dryer. Nominal drying gas rate: 360 kg/h.

Customized solutions for specific needs

GEA's PHARMA-SD® platform allows a high degree of customization to adapt to specific needs and we offer a range of options, components and add-ons to meet unique demands.

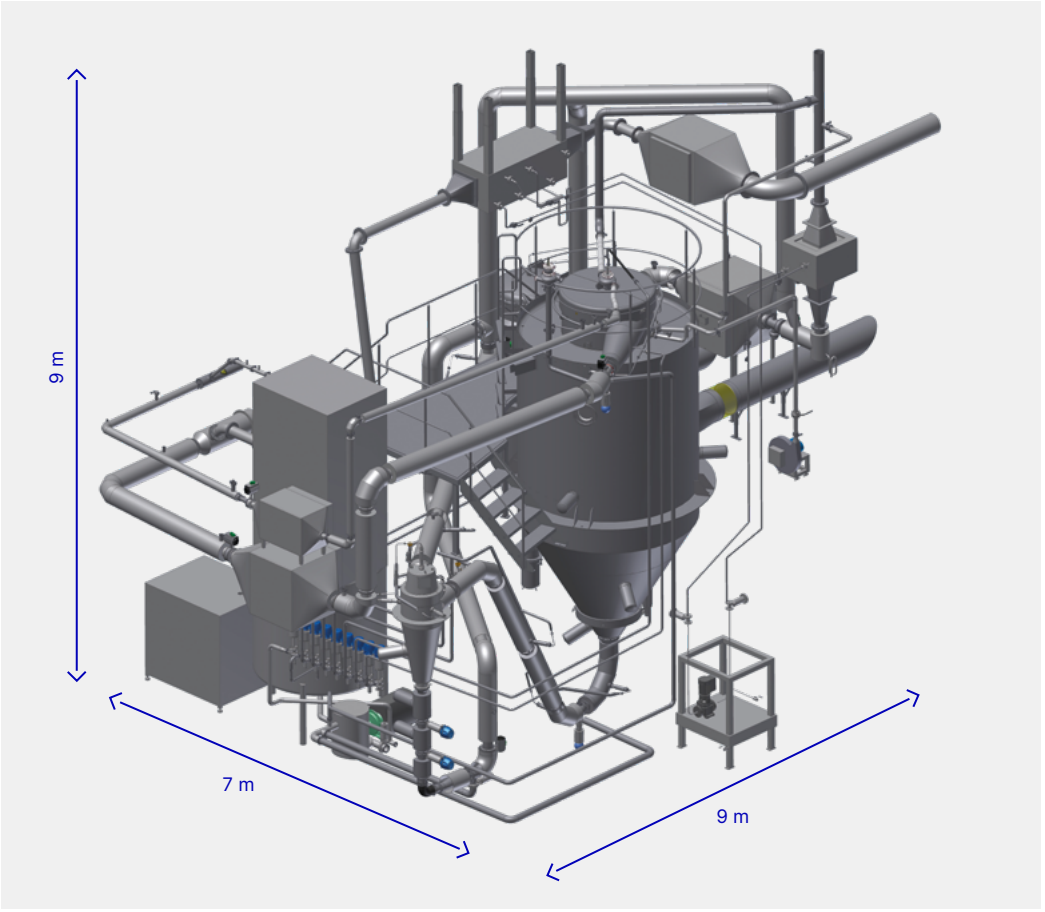
Our PHARMA-SD® spray dryer, for example, has been customized to produce powder with low bio-burden for terminal sterilization. In other cases, the physical properties of the API or the CQAs are so challenging that custom designs arise from test work.

Especially in the case of larger spray dryers, installations need to be adapted specifically to your site. Integrating feed preparation systems, powder handling equipment and Clean-In-Place (CIP) liquid skids is carried out by exchanging 3D drawings with your project group.

Large production facilities may use standardized instrumentation from a specific manufacturer, or the control system may have to be integrated with your SCADA system. GEA engineers are familiar with such requirements and work in close cooperation with your specialists to design optimal solutions.

Custom-designed PHARMA-SD® type PSD-1 spray dryer in clean room.

Powder collection in clean room, PHARMA-SD® type PSD-4.



Custom-designed PHARMA-SD® type PSD-3 with explosion vent panels, automatic Clean-In-Place system.

A sure path to healthy business

At GEA we know there is a lot more to formulating drugs than having the right equipment.

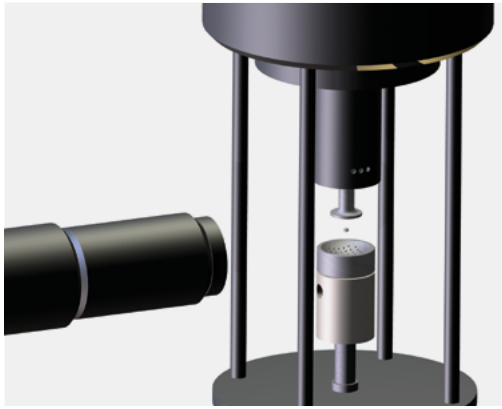
That is why we have never considered ourselves an equipment supplier but rather a process development partner. We can help with all aspects of investigating how spray drying could enhance your drug formulation.

Our capabilities span everything from reviewing particle characteristics right through to process development and large-scale test production. Customers gain a secure outcome, powder test materials and reduced time to market.

Beyond steel
Apart from hardware, collaborating with GEA also gives you access to the greatest concentration of industrial drying experts in the world. You'll find analysts versed in assessing and refining particle design; process engineers practised in overcoming the difficulties of scaling to commercial production; and people familiar with some of the intricacies of regulatory procedures.

Hands-on know-how in GMP spray drying
GEA has been pioneering spray drying as a unique enabling technique within the pharmaceutical industry. An important step was the inauguration of GEA's own GMP spray drying facility. Since 2004, the facility has been approved by the Danish Health and Medicines Authority to spray dry human medicinal products for clinical trials and later, also commercial use. Today spray drying is well accepted, and many pharmaceutical Contract Manufacture Organizations are now offering their services using GEA's PHARMA-SD® spray dryers. The expertise obtained from establishing and running a cGMP spray drying facility has been invaluable to GEA in the support of our customers. The success is incontestable but when it comes to offering GMP services, GEA will now leave that to our customers.

Product development process
Spray drying projects begin by listening to a customer's product aspirations. Once we understand these objectives we can recommend a process for achieving the desired result.



Bench analysis and trials
In the early drug development phase, when only a very limited amount of material is available, single droplet drying is ideal for testing the feasibility of spray drying and to address basic formulation questions. With GEA's DRYNETICS® and our spray drying expertise, only a few mL of feed material is needed to examine the morphology and to establish the basic spray drying process parameters.

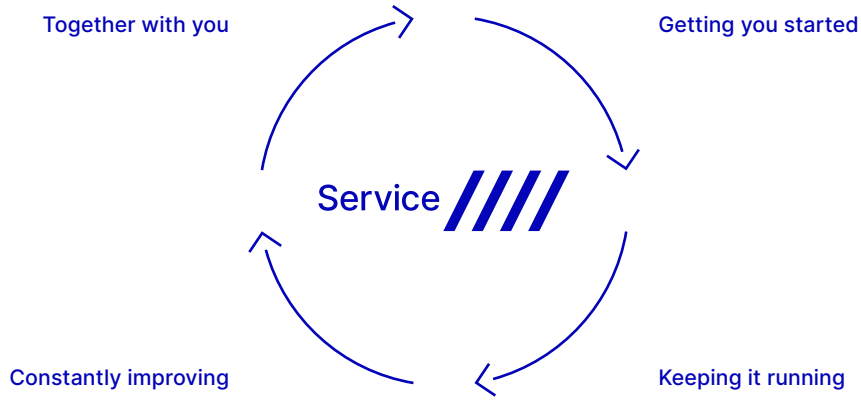
Small-scale pilot tests
A step further, we can develop the optimum spray drying process and make samples for technical analysis. With NIRO® spray dryers in several sizes available, we can produce samples in a capacity of a few grams/hour up to several kilos/hour – sufficient for technical analyses and product development.

Scale-up
Before turning to GMP testing, we make final process adjustments by running largescale plants at a similar capacity as the final production plant.

FOR YOUR CONTINUED SUCCESS.

GEA Service offers dedicated teams of service experts. Our focus is to help our customers build, maintain, and improve their performance, market presence and competitive edge for the entire life cycle of their plants and equipment.

Partnering with GEA gives you the benefit of our world-renowned, customer-tailored service and recommended spares upgrade, modernization and optimization services. With our support you can be certain that every piece of GEA equipment and technology will operate optimally from day one, and for its complete lifespan, to give you maximum return on your investment.



Getting you started –
Seamless support for instant productivity and performance

Keeping it running –
The cost-efficient way of ensuring safety and reliability

Constantly improving –
Sharing our knowledge to safeguard your investment

Together with you –
Enduring commitment to you and your business

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