Spray drying technology for better API crystals

The application of new techniques in spray drying of final product gives excellent control of particle size in API production. Filipe Gaspar and Jorge Manuel C. Pastilha of Hovione describe the latest technologies.

The interface between the manufacture of an API and its formulation into a pill, an injectable or inhaled drug is an area fraught with complexity – API particle size and crystal form have a direct impact on the performance of a drug, and yet in the list of the top contractors for custom synthesis there appears to be surprisingly few that claim to have any expertise in this area.

One explanation for this state of affairs may be the tradition that large multinationals have to keep the last step of the API in-house. The one manufacturing strategy that all pharmaceutical multinationals appear to have in common is the location of the final stages of the API synthesis in Puerto Rico, Ireland and now Singapore. This fiscal focus has caused most contract manufacturers of APIs to remain dedicated to supplying advanced, cGMP-compliant, intermediates to Big Pharma. They have therefore had little opportunity to develop know-how around the physical attributes of the final API.

The emergence of Small Pharma has inverted this trend. Those offering custom synthesis are now expected to deliver everything related to the API – this includes analytical chemistry, synthesis route innovation coordinated with raw-material sourcing, process development, regulatory filings and manufacturing in an environment characterised by compliance and service orientation – included, but often neglected, is the ability to speak the language of the next link in the chain: the formulator. Chemists and engineers do not, by training, recognise the challenges that formulators face in taking their API forward and turning it into a successful drug. Hovione has been making nothing but final APIs for more than 40 years, and as such the company has been acutely sensitive to the technical requirements of those that use the APIs it makes.

In line with the latest developments in spray-drying technologies and with the increasing demand for highly defined particle properties in the pharmaceutical industry, Hovione has installed and commissioned a state-of-the-art spray-drying unit able to operate under the most stringent cGMP conditions at its manufacturing plant in Portugal. The multipurpose unit is fit to deliver injectable grade APIs and is configured to be 'cleaned-in-place', discharging into a classified clean room.

Benefits of spray drying in pharmaceutical fine chemicals

The service of an API manufacturer not only involves the development of the chemical process and the supply of high-quality API, when and where required, but also paying close attention to those physical parameters that make up the necessary requisites for a successful formulation. Chemical skills must be complemented by a pharmaceutical culture. For a successful custom synthesis partnership it is imperative that the API contractor be both cognisant of the importance of having the product with the correct particle properties, and be able to develop a process that delivers it consistently. It is well known that properties such as particle size distribution and morphology affect important parameters such as bioavailability, dose uniformity and formulation. This is key in many galenic forms; in the field of inhalation for instance it is absolutely critical; it can also be the source of many last-minute surprises and frustrations until the situation is well controlled.

APIs are typically produced by extraction or chemical syntheses and most often isolated through a multiple-step process comprising controlled crystallisation, solid-liquid separation and drying. A post-drying step such as micronisation is frequently needed to adjust particle properties such as size distribution and bulk density. Some pharmaceutical compounds are particularly difficult to micronise by conventional grinding or jet milling. For example, materials that have low melting point or that are waxy can smear or form amorphous (and size-unstable) particles.

Spray drying is presently one of the most exciting technologies for the pharmaceutical industry, being an ideal process where the end-product must comply to precise quality standards regarding particle size distribution, residual moisture content, bulk density and morphology. Already widely used for the manufacture of many consumer and industrial products such as instant food, laundry detergents, ceramics and agrochemicals, the growth in pharmaceutical spray drying was driven by a number of advantages over conventional multiple-step processes and competing particle reduction technologies. It allows not only the replacement, in many processes, of all the complex, time-consuming and yield-reducing isolation steps, but also the production of APIs with tailor-made particle properties.

Another advantage of spray drying is the remarkable versatility of the technology, evident when analysing the multiple applications and the wide range of products that can be obtained. From very fine particles for pulmonary delivery to big agglomerated powders for oral dosages, from amorphous to crystalline products and with the potential for one-step

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Discharge of final product into a classified clean room.

formulations, spray drying offers multiple opportunities that no other single drying technology can claim.

From very fine particles to agglomerates

Spray drying involves the continuous atomisation of the feed solution into a hot drying gas, most commonly air or nitrogen. The fine droplets resulting from the atomisation of the feed solution are immediately exposed to the drying gas leading to supersaturation and resulting in the formation of ultra-fine particles, typically below 5 microns and with a tight particle size distribution, which are collected via a cyclone (Fig 1). These highly defined particles have promoted spray drying as a method of choice for the production of powders for inhalation.

Moreover, technological developments in the construction of spray dryers have also stimulated the application of this technology in the production of agglomerates for the pharmaceutical industry. In the early 1990s, the spray dryer with integrated fluid bed became the most important spray drying concept in the food and chemical industries for producing agglomerated powders. Several large-scale plants were commissioned for the production of milk powder and soluble coffee and the concept was extended to the pharmaceutical fine chemical industry with the preparation of Captisol, a leading proprietary cyclodextrin that Pfizer uses in the formulation of its compounds Geodon and Vfend. The agglomerated powders are produced by re-introduction of the very fine particles into the drying chamber (Fig 2). The dry fine particles in contact with wet particles form agglomerates with enhanced handling properties. These dust-free agglomerates are free-flowing powders, which are far easier to dissolve in their final application, thus avoiding the formation of suspended lumps of product.

From amorphous to crystalline products

When starting from a product solution, spray drying is known to produce predominately amorphous material due to the almost instantaneous transition between liquid and solid phases. This is often desirable, as it may be used to increase the bioavailability of the resulting product. However, spray drying can also be used to obtain crystalline products with defined sizes and controlled residual solvent contents. To achieve such a goal, the product is fed in a crystalline suspension, instead of a solution, to the drying chamber. Feeding the crystals in the right form allows spray drying to fine tune crystal size distribution and final content of residual solvents. In between these two extremes it is also possible to manipulate the degree of crystallinity of the product, enhancing control over physiochemical properties and functionality of the final product.

Suitability for heat-sensitive products

Contrary to a general misconception, spray drying is a very gentle drying technology when dealing with thermally labile compounds. The shielding effect of the solvent during drying protects the product contained in the core of the fine droplets from the bulk temperature in the drying chamber, typically between 70 and 150ºC. In addition, exposure time is extremely low, usually a few seconds, minimising the heat 'shock' and the potential degradation of the product molecules. The gentleness of the drying process together with the ability to provide highly defined particles with tunable properties and the lower processing costs makes spray drying a true and economic alternative to freeze drying when handling heat-sensitive products.

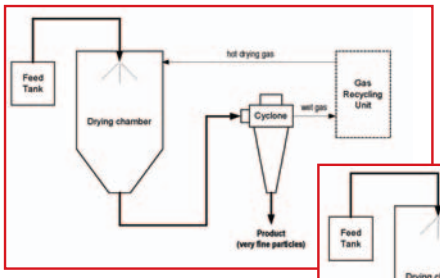

Fig 1. Very fine particles from spray drying.

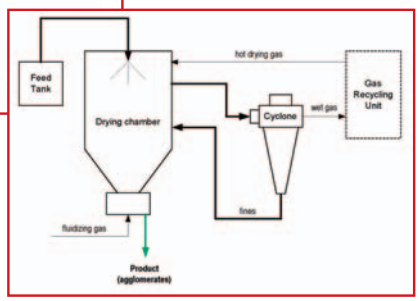

Fig 2. Agglomerates from a fluidised spray drying system.

cGMP spray drying – multipurpose application across a range of scales

Hovione's fully automated unit operates under the most stringent cGMP conditions and can be configured both as a conventional spray dryer for the production of very fine particles (< 5 to 10 micron) and as a fluidised spray dryer when producing agglomerated, free-flowing dustless materials (100 to 400 micron). The facility allows continuous production of dry solids in either powder, granulated or agglomerated form from liquid feedstocks such as solutions, emulsions and pumpable suspensions.

Hovine's services in process chemistry and manufacturing span the complete range of scales – from lab to pilot to commercial scale, and spray drying can be carried out across all of them at the company's sites. sp²

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FURTHER INFORMATION

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