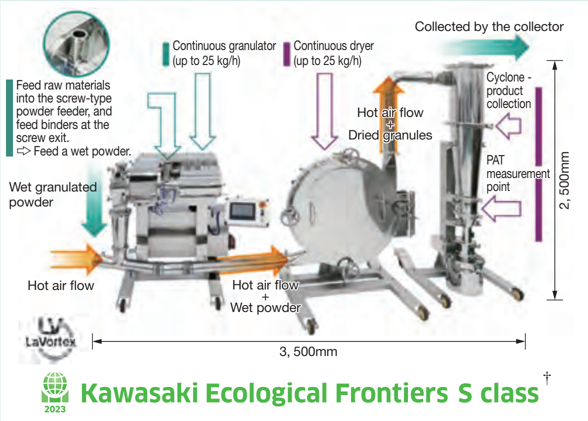
Continuous Granulation and Drying System for Pharmaceutical Powder LaVortex



The majority of solid pharmaceutical preparations (tablets and granules) are still manufactured using batch methods. However, the introduction of continuous production methods is being considered because of the advancement of sensor technology and government policies. We have developed LaVortex, a continuous manufacturing system capable of continuous granulation and drying of pharmaceutical powders. This system consists of LaVortex G, a continuous tube-rotating agitation granulator, and LaVortex D, a continuous air flow dryer. Compared to the conventional batch agitation granulation method and the fluidized bed granulation method, our system can continuously produce granules with properties superior for tablet compression, thereby facilitating mass production.

Introduction

In 2014, the U.S. FDA (Food and Drug Administration) published the ICH Q13 guidance for transitioning pharmaceutical production from conventional batch processing to continuous production processing. In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has also announced a policy that encourages transitioning to continuous production. In conjunction with the advancement of sensor technology and government policies, this has led pharmaceutical manufacturers to consider introducing continuous production.

1 Background

The majority of solid pharmaceutical preparations (tablets and granules) are manufactured using batch methods, by which raw materials are fed into and discharged from equipment all at once, but their production efficiency is improving more slowly than methods in other industries. This is because with respect to production methods in which raw materials are continuously fed to continuously produce products, it is difficult to enforce conformity to the strict quality control standards applied to pharmaceuticals. To meet these standards, it is necessary to implement technology for constantly monitoring and controlling a continuous flow of raw materials and products throughout the process; such technology is referred to as a high-precision Process Analytical Technology (PAT). In continuous production methods, the manufacturing volume can be adjusted by changing the duration of operation. Other advantages include eliminating the need for scale-up considerations when transitioning from the development phase to the commercial production phase.

To facilitate continuous processing, we have developed LaVortex, a continuous production system for granulation and drying, which are the most important steps for manufacturing solid pharmaceutical preparations.

2 Product overview

As shown in the diagram, the continuous production system LaVortex consists of the continuous granulator LaVortex G and the continuous dryer LaVortex D, which together carry out the continuous granulation and drying of powder as well as produce dried granules from raw material powders and liquid binders. LaVortex supports a wide range of throughput rates for standard pharmaceutical prescriptions, from 2 to 25 kg/h.

† A completely continuous pharmaceutical production system that replaces a traditional batch manufacturing system with a continuous production method in order to control production quantity according to demand, stabilize production, and implement advanced quality control.

A raw mixture of active ingredients and other additives is fed into LaVortex G as a wet powder by feeding liquid binders into the screw-type powder feeder. The wet granulated powder continuously falls into the hot air pipe immediately beneath LaVortex G, is transported by a hot air flow, fed into LaVortex D, passes through the continuous drying unit while being dried, and then is collected by the cyclone. The PAT equipment installed in the lower part of the cyclone continuously measures the moisture content and diameter of the dried granules. The diverter valve operates in accordance with the quality determined from the measurement results, transporting only conforming granules to the next process.

3 Product features

(1) Features of the continuous granulator LaVortex G

The structure of LaVortex G's continuous granulation unit is shown in **Fig. 1**. It adopts the tube-rotating agitation method, which makes use of our expertise in batch agitation granulators. The chopper blades and the rotation tube rotate in the same direction. The high-speed rotation of the chopper blades and the low-speed rotation of the rotation tube facilitate granulation. A wet mixture of raw powders and liquid binders is fed into the feeding port, transported to the continuous granulation unit by the screw, and agitated by the rotation of the chopper blades and the rotation tube with their axes of rotation being offset from each other. In the lower part of the continuous granulation unit, the chopper blades are positioned closely to the rotation tube so that the chopper blades are structurally more likely to make contact with the wet powder moving near the wall of the rotation tube. By contrast, in the upper part, the two partition plates separate the continuous granulation unit so that the wet powder stays longer. In addition, the chopper shaft also has two disks, not blades, at positions near the aforementioned partition plates. Combined, these help the wet powder stay longer in the continuous granulation unit while sizing it. The wet granulated powder that passes through the continuous granulation unit is continuously discharged from the discharging port and transported to the next step.

(2) Features of the continuous dryer LaVortex D

LaVortex D consists of a two-layered spiral drying chamber. The structure of its continuous drying unit is shown in **Fig. 2**. The wet granulated powder discharged from LaVortex G is transported by a hot air flow, dried while passing through the 10-meter-long continuous

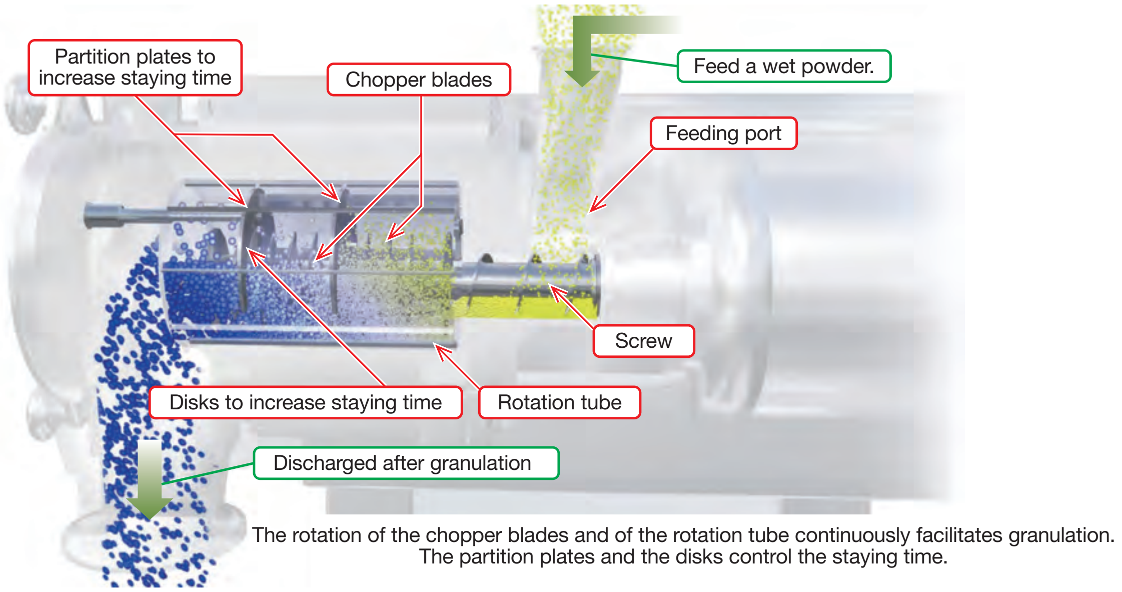
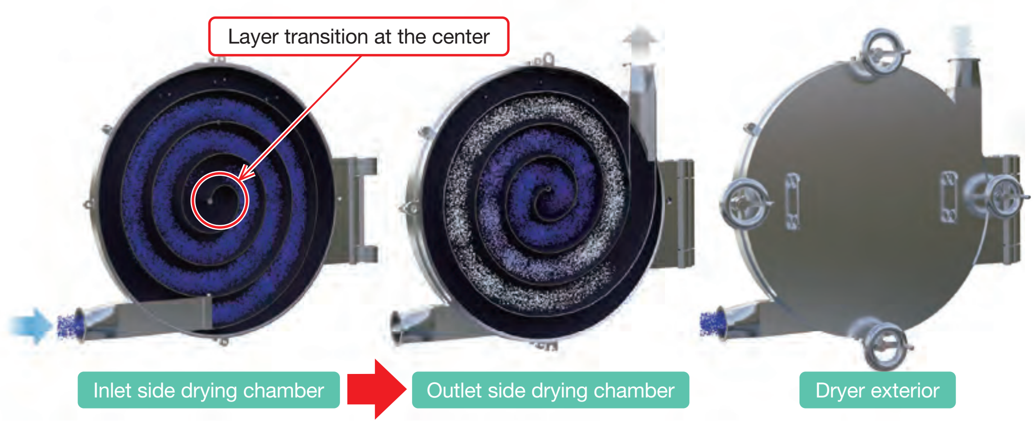


Fig. 1 Structure of continuous granulation unit



To divide the unit into two layers, there is an intermediate plate between the inlet side and outlet side drying chambers.

Fig. 2 Structure of continuous drying unit

drying unit, and collected by the cyclone. The drying unit is divided into two layers, namely the inlet side drying chamber and the outlet side drying chamber, which face each other across an intermediate plate. A spiral-shaped plate is affixed in each drying chamber to create a two-layered spiral air flow channel. The hot air flow and wet granulated powder flowing from the hot air pipe enter the periphery of the inlet side drying chamber and pass through the channel that leads to the center of the spiral. After reaching the center of the spiral, they proceed to the outlet side drying chamber through the hole in the intermediate plate and then pass through the channel that leads outwards from the center of the spiral. This realizes a structure that makes the walls of the drying channel, which contact with the outside, small in area and reduces radiation loss. After reaching the outermost periphery, the dried granules are discharged from the continuous drying unit and then collected by the cyclone.

The dried granules are continuously measured by the PAT equipment installed in the lower part of the cyclone. As the PAT equipment, a near infrared spectroscopy and a particulate probe capable of nondestructive measurement are installed to measure the moisture content, particle diameter, and particle size distribution in real time. To precisely measure the moisture content using near infrared spectroscopy, dried granules are temporarily accumulated by the diverter valve and semicontinuously measured in small quantities. The diameter is measured completely continuously without accumulating the granules by means of a measurement nozzle installed in the cyclone channel. This measurement confirms that the granules produced by LaVortex are of uniform quality.

(3) Comparison with conventional granulation methods

Table 1 shows a comparison between the granulation and drying method employed for LaVortex and conventional batch methods, namely agitation granulation and fluidized bed granulation, under the condition that the processing volume is 25 kg/h. The particle size distribution breadth and bulk density of granules produced by LaVortex fall between those of granules produced using

Table 1 Comparison with conventional granulation methods

Granulation method	①「LaVortex」	② Agitation granulation	③ Fluidized bed granulation
Production method	Continuous	Batch	Batch
Particle diameter d10 〔μm〕	58. 4	62. 9	62. 2
Particle diameter d50 〔μm〕	181. 0	197. 9	125. 1
Particle diameter d90 〔μm〕	537. 8	670. 3	234. 2
Particle size distribution breadth	Medium	Broad	Narrow
Bulk density 〔g/mL〕	0. 547 medium	0. 730 high	0. 390 low
Tablet hardness 〔N〕	70 appropriate	35 low	75 appropriate

Fig. 3 Granular shape and surface condition

conventional methods. In addition, LaVortex produces granules that are spherical and easy to process, like those produced using the agitation granulation method, as shown in **Fig. 3** while exhibiting appropriate tablet hardness (the force required to break a formed tablet), like those produced using the fluidized bed granulation method. Thus, LaVortex can continuously mass-produce granules with excellent tablet hardness that can easily be formed into tablets.

Conclusion

We are currently promoting LaVortex not only in the pharmaceutical industry but in the food and chemical industries. We are also developing a continuous manufacturing system for mixing pre-granulated raw materials for the stages preceding and succeeding granulation and drying.

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