HOSOKAWA MICRON GROUP

FORMULATION METHODS & SIZE REDUCTION FOR INHALERS

In this summary article, Bert Dekens, Team Manager, Pharma, Hosokawa Micron, highlights the importance of achieving the correct particle sizes, both for the API and the carrier (which are each required at different sizes) in formulations for inhalation, and describes some of the available equipment most suited to specific tasks.

Dry-powder inhaler formulations typically comprise a combination of a carrier substance with the active pharmaceutical ingredient (API). Sometimes additives are required to enhance the product properties, such as flowability, or to support the mechanical bonding of carrier with API.

The carrier material, often lactose, represents a high proportion of the final product and is often required to be of coarser particle size in the range of 40-200 µm. The API is only a small percentage of the inhalable formulation and needs to be of finer particle size, mostly in the single micron range.

APIs are very often cohesive, poorly flowing powders and sometimes a really tight particle size distribution is required. Special attention has to be paid to the amorphous content of the API.

> "API is blended with carrier particles which are prepared to have a defined surface area and surface energy"

Like in any another drug production, the actual manufacturing process, including crystallisation and drying cannot be sufficiently controlled and influenced to achieve the required particle size. Additional steps – in some cases only de-agglomeration after the dryer or real grinding – needs to be done to get the right particle size for inhalation.

Particle size is cited as being the single most important design variable of a DPI formulation.[1]

When choosing suitable milling equipment, it is necessary to characterise the different powders that are to be processed. Product properties such as hygroscopicity, flow properties and bulk density, among others, influence which types of mill are suitable.

API

Spiral Jet Mills

The most common jet mill used in pharmaceutical industry for micronisation of fine particles is the spiral jet mill or pancake mill. The particles fed to the grinding chamber are accelerated by the high gas flow (typically in the range of 4-8 bar g) and particles are crushed by collision with each other as well as partly at the walls of the grinding chamber. Due to the fact that there are no movable parts, no drives etc, they are relatively easy to inspect and clean. In general, jet mills do not create heat during grinding which is advantageous since many pharmaceutical powders are heat sensitive. Due to the above points, maintenance of these mills, and operation under contained conditions, are simple.

Spiral jet mills come in many sizes, depending on required capacities or batch sizes.

Opposed-Jet Mills

Alternatively the opposed-jet mill (see Figure 1) can be used, whereby product is fed to the mill gravimetrically and falls into the grinding chamber. There the particles get accelerated by the fast gas stream and grinding takes place by particle to particle collision.

The ground particles are offered to the integrated air classifier. The air/gas flow has to go through the shown lamellas. The particles are subject to two forces. The

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Figure 1: The 280 AFG Fluidized Opposite-Jet Mill.

drag force of the air – and the centrifugal force of the classifier wheel. Fine particles rise with the air whereas coarse particles are rejected by the classifier and drop back into the mill. High classifier speed means fine end product, low speed means coarser product. These classifiers are typically most suitable for particle sizes in the range 5-150 µm (Figure 2).

CARRIER

The carrier material is often lactose. To achieve the required properties such as the optimum flowability, the particle size distribution – for the carrier as well as for the API – is crucial. Depending on the type of applicator, the optimum fineness might be in the range of 40 µm or can be up to 200 µm. A high

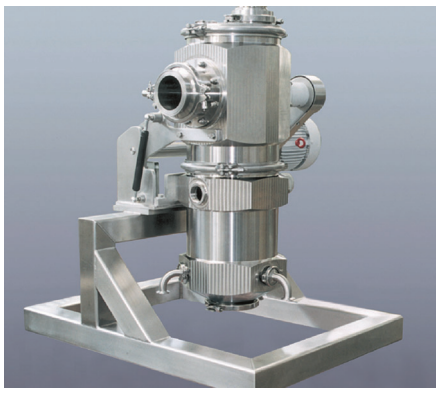

Figure 2: The 200 ZPS Classifier Mill.

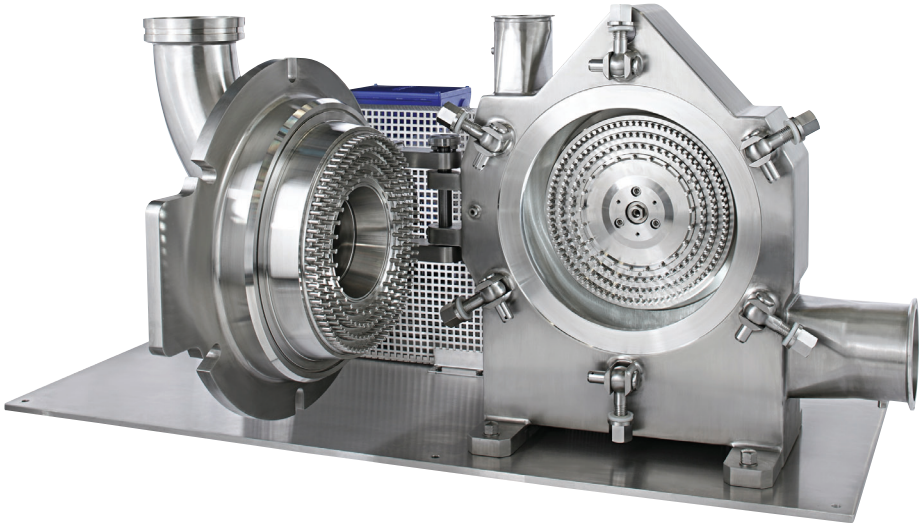

Figure 3: 315 UPZ Fine Impact Mill, Pharma Execution.

content of fine dust is normally not allowed and therefore the production of the carrier is often a combination of milling, classifying and sometimes blending steps. The fact that the carrier material is mostly coarser than the API requires typically a different mill type.

The difference between the different fluid energy impact mills used for the API compared with those used for the carrier is that the speed to which the carrier particles are accelerated is much lower, therefore the achieved particle size is coarser.

fine end of the particle size distribution. The principle is more or less the same. The material is gravimetrically fed to the classifier from the side or from the top. There is an airflow created by a blower. The feed material will be dispersed in air/gas and then offered to the classifier. Coarse material will be rejected and will drop to the bottom where the coarse fraction (in this case the final product) is collected. The fine fraction will leave the classifier and is separated at a filter.

> "The flowability of the formulated material, as well as the fluidisation properties together with the entrainment and separation characteristics determine the physical behaviour of the formulation in the inhaler"

Those mills are suitable for medium-range finenesses and the advantage is that they can be equipped with a number of different grinding tools suitable for different products and requirements.

As an example, pin mills are used for fine grinding of lactose. Typical finenesses are around 300 µm and the typical maximum fineness with lactose is around 90% <75 µm.

When steeper particle size distribution or higher-end fineness is required, an impact mill with an integrated air classifier might have advantages (Figure 3).

The fact that no significant amount of fine dust is allowed very often leads to a second classifying step to remove the very

As we have seen with the jet mills, a typical mechanical impact mill can also be combined with an air classifier. The operating principle is similar.

FORMULATION

The finely ground API is blended with carrier particles (excipients) which are prepared to have a defined surface area and surface energy. To achieve an even layering of API particles, an appropriate blender with the correct operational parameters needs to be selected (Figures 4 & 5). This allows for the proper handling (transportation, storage and dosing) of the API's,

Figure 4: High-Shear Blender, Five Litre Cyclomix, Pharma execution.

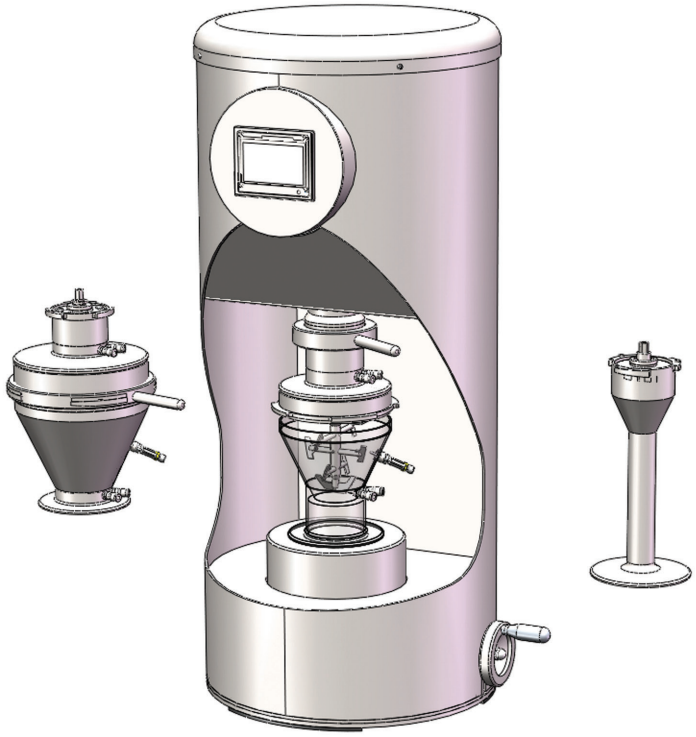

Figure 5: Lab-Scale High-Shear Blender with Exchangeable Product Bowls.

which is typically a cohesive powder and normally fairly difficult to work with, especially in the smaller quantities needed.

Phenomena related to the interaction between the carrier particles and the API play an important role in the final quality of the product. The blending properties and surface characteristics of the carrier particles will affect the bonding between API and the carrier. The flowability of the formulated material, as well as the fluidisation properties together with the entrainment and separation characteristics determine the physical behaviour of the formulation in the inhaler device.

In order to obtain the right formulation a balance has to be found between the sufficient mixing energy required to disperse the API, as single particles within the bulk carrier particles. On the other hand the mixing energy cannot be too high since this could lead to possible damage of the carrier particles resulting in undesirable variations in the product characteristics.

Similarly the bonding of the API particles onto the surface of the carrier particles has to be sufficiently strong to form a stable formulation. Just as above with the mixing, the bonding strength has to be such that while providing the proper handling characteristics it also needs to be capable of releasing the API while being inhaled in order for the API to be delivered as required.

Hence this will necessitate a dedicated mixing process as well as a proper selection and manipulation of the powder properties associated with the DPI formulation. The overall mixing mechanism takes care of the distribution of one component within the other. Key here is to be able to transport particles throughout the mixture. Optimal mixing is achieved when the different components can randomly be distributed.

To summarise, the advantages of a high intensity impact and shear mixer include:

- Perfect dispersion of fines due to the combination of impact and shear mixing
- Accurate temperature control with jacketed vessels
- Rounding-off or densification of particles possible
- Single layer coating achievable
- Create homogeneous mixture without lumps
- Reproducible processes
- With the conical design vessel, filling rates between 30-100%
- Full discharge through the central bottom discharge valve
- CIP and SIP able designs

CONCLUSION

In conclusion we have reviewed the different technologies available for the size reduction of API and carrier particles as well as mixing technologies available for proper formulation of the final DPI product.

REFERENCE

1. Telko MJ, Hickey AJ, "Dry-Powder Inhaler Formulation". Resp Care, 2005, Vol 50(9), pp 1209-1227.