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Process technologies for tomorrow.

ONE-STOP SHOP FOR TOTAL MIXING SOLUTIONS FOR PHARMACEUTICAL MANUFACTURERS

Here, Bert Dekens, Application Manager at Hosokawa Micron, discusses the company's offering for pharmaceutical powder mixing, including the Cyclomix high-shear mixer and the Nauta low-shear mixer, and how the company's technology solutions take a broader approach to the full mixing process than simply providing a mixing machine.

Hosokawa Micron has long-standing and proven experience of developing scalable powder-mixing technologies for the pharma industry, ranging from R&D to large-scale manufacturing set-ups. The company's technology offering includes the Cyclomix, which is widely used for the high-shear mixing of cohesive dry powder inhalers (DPIs); the Conical Paddle Mixer (CPM) for mid-shear mixing; and the Nauta conical screw mixer.

CYCLOMIX – HIGH-SHEAR MIXER

Blending formulations for DPIs is a delicate matter. Inhalable dry powder APIs often require lactose carriers in order to achieve the desired aerodynamic properties for delivery into the lungs, and so these two ingredients need to be carefully mixed. To disperse the fine API particles amongst the carrier, one needs to break up the cohesive forces between them, which requires a certain mechanical energy. However, if the energy applied to the formulation is too high, the adhesive forces between the carrier and the actives will also be too high, which limits separation during inhalation.

Finding the right balance for the required mixing energy is a critical issue for processing DPI powders and calls for a very efficient mixer. Hosokawa Micron's Cyclomix blending technology (Figure 1)

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Figure 1: The Cyclomix blending technology for high-shear blending of DPI formulations.

is a proven product on the market for high-shear blending of DPI formulations. Cyclomix has proven to be very effective for tuning mixing energy to the delicate adhesion/cohesion balance and providing a homogenous blend without particle deterioration. Multiple systems have been sold and delivered for this challenging application.

Cyclomix systems are modular and – besides offering exchangeable product bowls – can be tailored to local requirements by combining options. In order to offer the optimal product to its customers, Hosokawa Micron provides the Cyclomix in three platforms suited to the intended powder batch size, including laboratory scale (Figure 2) for 100 mL, 1 L and 2 L batches; mid-range for 5 L and 15 L batches; and large-scale able to handle batches of up to 100 L.

NAUTA – LOW-SHEAR MIXER

When it comes to mixing ingredients for industrial-scale production of tablets, many pharmaceutical manufacturers opt for wet or dry granulation to minimise the risk of



Figure 3: Nauta mixer for pharmaceutical applications.

Figure 2: Mini Cyclomix lab mixer.



segregation. Direct compression is actually a simpler and more affordable alternative to this approach. However, this approach requires manufacturers to adapt their strictly defined, validated and documented procedures. The amount of time, money and administrative effort this entails can often discourage them from switching to the direct compression method. Nevertheless, the time and cost savings made possible by the use of the Nauta mixer can make that extra effort worthwhile.

Today, the tablet is the most common dosage form for medicinal products. Pharmaceutical manufacturers must adhere to high quality standards and regulations to guarantee that each tablet contains exactly the right ratio of API to excipients, such as binders, lubricants, flavourings and pigments. To achieve this, all the components must be mixed optimally before being pressed into tablet form. Many manufacturers mix the ingredients in a tumbler or container mixer and then perform either wet or dry granulation to reduce the risk of them separating again afterwards. However Hosokawa Micron's Nauta mixer (Figure 3) offers the best of both worlds. By combining direct compression with the avoidance of segregation, it can eliminate the need for granulation, thus saving pharmaceutical manufacturers time and money.

Wet and Dry Granulation

In general, the risk of segregation is minimised by reducing the differences in

bulk density and particle size distribution between the APIs and excipients. To accomplish this, manufacturers often implement a granulation step to reduce this risk. Wet granulation involves multiple steps, such as granulation, drying and screening. As such, it is a time-consuming, and therefore cost-intensive, process. Alternatively, dry granulation can be used, especially when the product to be granulated is sensitive to moisture and heat. Although dry granulation is simpler, and therefore less costly than wet granulation, it often produces a higher percentage of fine granules, which can compromise the quality of the tablet.

Advantages of Direct Compression

A growing number of pharmaceutical manufacturers are discovering that direct compression offers a simpler, and therefore cheaper, alternative to granulation techniques. It entails the mixing of dry, free-flowing powders with a uniform particle size so that they can be directly compressed in a tablet press. The Nauta mixer is capable of eliminating the granulation step by enabling direct compression.

Despite being well-known and having been first developed several decades ago, the Nauta conical screw mixer has been continuously improved in line with the very latest technological advances to keep it constantly up to date with the needs of customers in the pharma industry. It is ideal for the low-shear mixing of delicate free-

flowing powders, enabling all the necessary ingredients to be blended into a completely homogeneous mixture to ensure uniform and high-precision dosages. Moreover, the Nauta is hugely flexible in terms of the filling volume, producing an excellent mixing result even if the mixer is only 10% full. This also makes it suitable for use in a multi-staged mixing process to produce low-dose tablets.

TOTAL MIXING SOLUTION

Hosokawa Micron, rather than simply supplying machines, also takes a broader approach to design a total mixing solution that integrates the pre- and post-processes (Figure 4). This entails a full consideration of four aspects:

- How the powder is fed into the mixer
- What happens inside the mixing vessel
- How the powder is discharged
- How the equipment is cleaned.

For the charging and discharging of toxic materials, for instance, Hosokawa Micron can use or develop customised container docking systems, such as lift systems or split butterfly valves (Figure 5).

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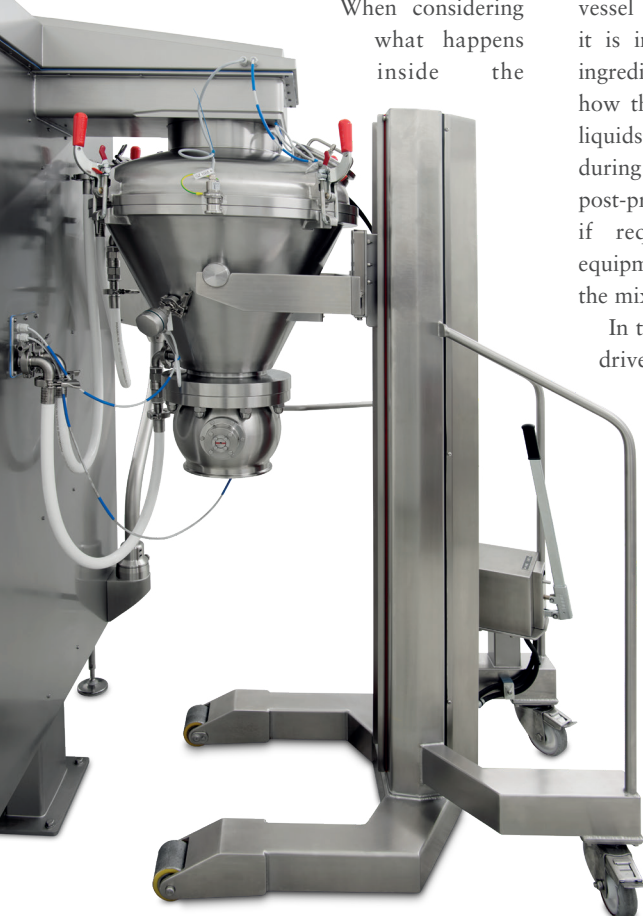
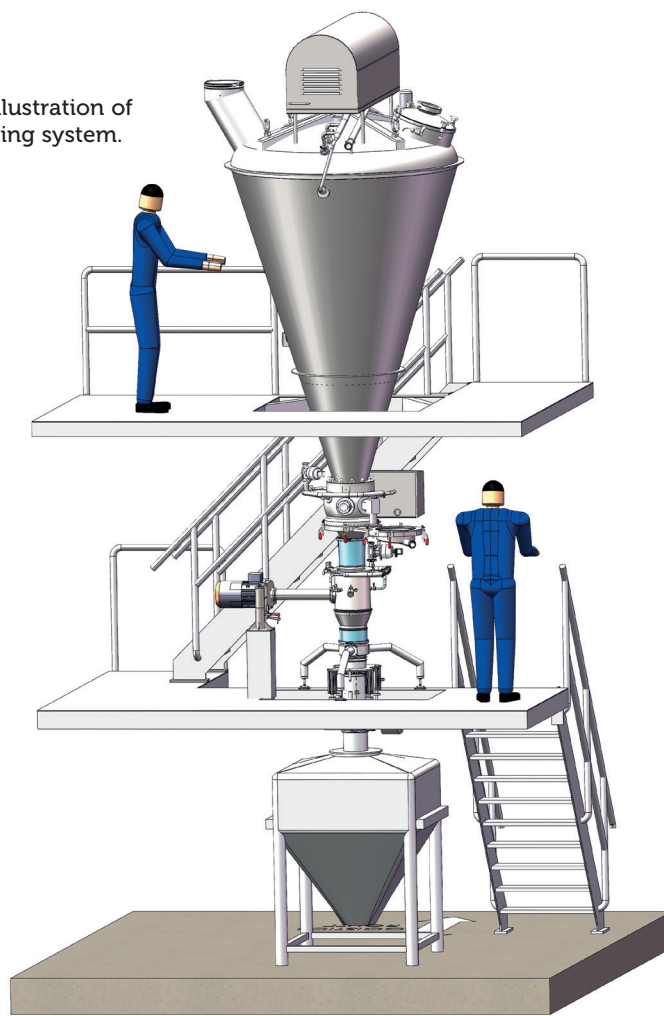


Figure 5: Lift system for conical mixers.

Figure 4: 3D illustration of a pharma mixing system.



vessel during the mixing process itself, it is important to take into account any ingredients the customer may need to add and how they will affect the process, including liquids, which can even be heated or cooled during mixing if necessary. Additionally, post-processing equipment can be integrated if required, such as deagglomeration equipment, sieves, cone mills, etc, to turn the mixture back into powder.

In the Nauta, the conical vessel and top-driven agitation ensure that the powders will not segregate again during discharge into a tablet press, which can be a problem when container mixers are used. If desired, it can even be positioned right above a tablet press to ensure direct discharge, further contributing to maintaining the stability of the product.

The fourth aspect, cleaning, is of critical importance in the pharma industry, which is why Hosokawa Micron offers complete automated cleaning in place (CIP) and sterilisation in place (SIP) installations, including the associated control systems (Figure 6). In order to eliminate

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the handling step and thereby reduce the risk of product contamination and increase operator safety in the case of toxic materials, the CIP and SIP skids on Hosokawa Micron machines are permanently docked. Needless to say, all the systems comply with the applicable regulations and guidelines, and come with the relevant documentation to prove it, relieving the regulatory burden on customers.

SMALL-SCALE PRACTICAL TRIALS

Time is of the essence for manufacturers striving to win the race to market and secure the all-important patent for an original pharmaceutical product. In order

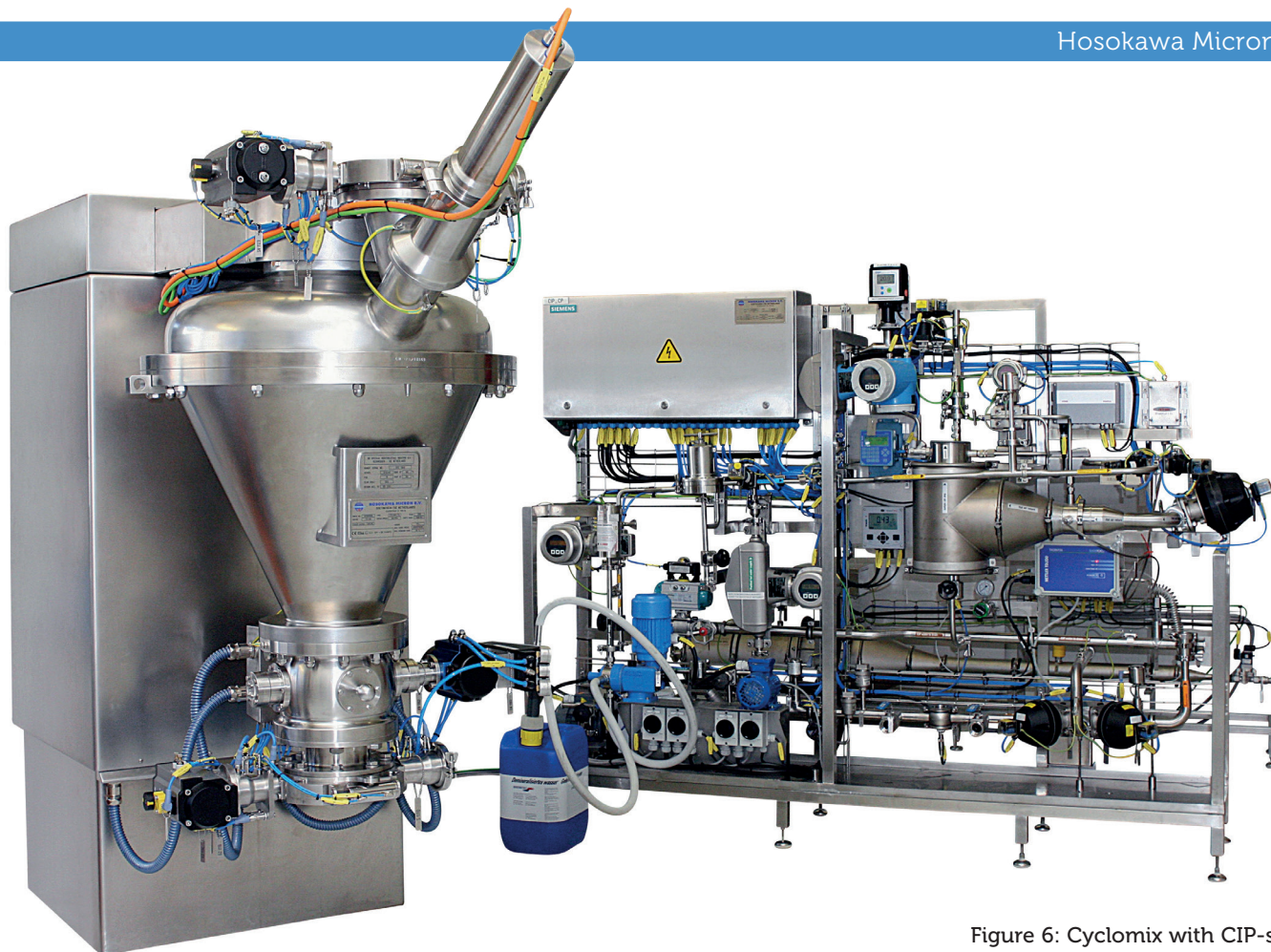


Figure 6: Cyclomix with CIP-skid.

to optimally explore the cost-saving possibilities provided by switching to direct compression, it is advisable for pharmaceutical partners to contact Hosokawa Micron as early on as possible – preferably during the R&D process. After all, the formulation of each new tablet is unique, so a product-specific solution is developed together with each customer.

For example, it could be beneficial for a formulation to add the excipients directly into the same mixer as the pre-mix, rather than splitting this up into individual process steps. This is precisely what the Nauta mixer facilitates. Hosokawa Micron's test centre in the Netherlands – which, thanks to its size and wide range of capabilities, is unique in Europe – enables the company to work closely with customers to investigate such possibilities using the actual ingredients in real-life, small-scale trials.

A second situation in which the direct compression approach makes sense is for generic pharmaceutical products. Generics manufacturers have to focus on reducing

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costs, even if it means they have to redesign their production process, including revalidating their procedures as necessary. The cost savings that can be achieved via direct compression without compromising on quality make it an extremely worthwhile consideration.

CONCLUSION

The energy required for powder mixing depends on various factors. The powder characteristics, such as the cohesion of materials and particle size, are important, of course, but other considerations include both the end-product properties and the process,

safety and system requirements. Due to Hosokawa Micron's wealth of experience and in-house technology, the company is a one-stop shop for mixing systems and is able to advise each customer about the best batch mixer solution – low, mid or high shear – for their particular situation.

ABOUT THE COMPANY

Hosokawa Micron is a global supplier of process equipment and systems for the mechanical and thermal processing of dry and wet powders. The company specialises in the design and manufacture of mixing, drying and agglomeration technologies.

Hosokawa Micron maintains extensive facilities for R&D, testing, manufacturing, toll processing and after-sales services, and has a total of around 170 employees. Hosokawa Micron BV is a wholly owned subsidiary of the Japanese Hosokawa Micron Corporation.

ABOUT THE AUTHOR

Bert Dekens is Application Manager, Pharma, for the Hosokawa Group, focusing on DPI-blending markets. Mr Dekens holds a key position in the DPI network within the International Hosokawa Group and is well established in the DPI market.