

Compact and efficient

Continuous mixing systems for the production of pharmaceutical tablets and granulates

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The Process Analytical Technology initiative demands the implementation of in-process monitoring systems and controls along with the mixing process. Gericke has developed continuous mixing and metering systems that meet the stipulated accuracy and the highest hygienic requirements. Own testing and model calculations demonstrate that their efficiency is determined not only by process parameters such as average residence time and metering constancy but also by the particle size distribution and the concentration range of the active substance.

Mixing processes in the pharmaceutical industry have grown out of traditional practices. With a multitude of regulations governing the industry, it is difficult to introduce technical improvements. Once a batch size has been defined and validated, it can no longer be changed. This rigid system has a number of disadvantages. The minimum production volume is determined by the batch size (such as 1000 l). In some cases the mixing process is validated up to three times prior to the approval of a new medication: at laboratory scale during preparation of the initial product for clinical testing, for the

pilot plant and for the final production system. Planning and implementation of a mixing process that has to be designed and validated threefold takes time and money.

The continuous mixing process is much more compact. Instead of, for example, a 1000 l batch mixer, continuous machines with a mixing chamber of only a few litres are used. Gravimetric metering systems for the base components (lactose etc.), excipients and the active substance components feed these components into the small mixer continuously. The capacity of the mixing process can be anything from 10

to 15 kg/h up to a maximum of 100 kg/h for blockbuster products. These compact units can be installed immediately above a tablet press or another granulation process. There is no interim storage and the mixing process can be matched perfectly to the continuous compaction process. It is conceivable that the same mixing process could be used to manufacture the product for the initial clinical trials and the subsequent actual production volume. The only variable is the production time, from a few minutes to several days. The batches are no longer determined by the size of the mixer but by the volume manufactured over a defined time. The tablet press (compaction) and the mixing system can be combined to form a single compact module. Similar processes have already been implemented for blockbuster products in Asia for some years. Although the patent protection had expired, efficient production was still essential. Other industries have been using continuous mixing processes for a long time now. The food and animal feed industries already have highly complex mixing tasks. Complex in this case means mixing tasks in which the components have very different flow properties or are only used in a very low concentration (vitamins).

Reduced flexibility plays no role

The advantages of a continuous mixing process compared to traditional batch processing are obvious: more compact plant dimensions with the same throughput, leading to simplified mixing due to the smaller dimensions and less complicated technology. The continuous mixing process is automated, and the recipe and throughput are generally distributed to the various gravimetric metering systems by the master controller. The major disadvantage of continuous mixing is its reduced flexibility to recipe changes. However, this lack of flexibility plays no role in the production of pharmaceutical blockbuster tablets. It is therefore not surprising that – particularly in Asia (with European equipment manufacturers) – highly efficient production processes have meanwhile been established. The US Food and Drug Administration reacted to this process after a certain delay before launching the PAT initiative (PAT = Process Analytical Technology). This working title refers to the continuous production and development of new measurement and analytical procedures which ensure that product quality and production conditions are recorded during the process. Gericke has extended its GCM continuous mixer series for very small throughput volumes to take account of this new pharmaceutical mixing



The GCM continuous mixer series has been extended with the GCM250

process with the name GCM250. The design of the mixing chamber and paddles guarantees defined axial and radial mixing. The residence time is controlled and typically lies between 5 and 50 s. The average residence or retention time of the particles in the mixing chamber is influenced by several process factors:

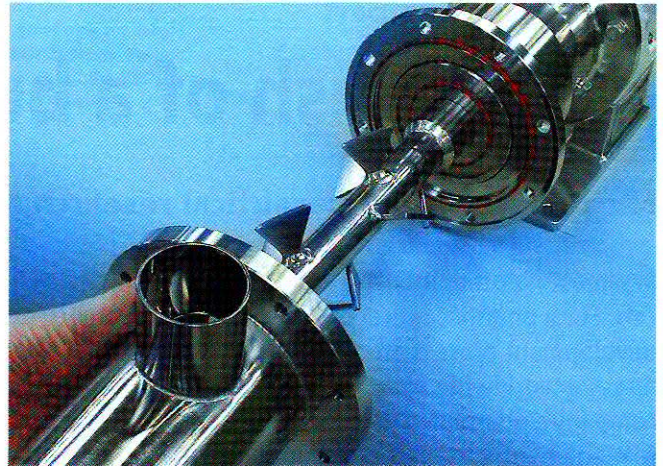
- The volume flow of the initial components, namely 20 to 500 kg/h. The higher the process output, the shorter the average residence time
- The degree of opening of a valve in the mixer discharge
- The rotation frequency of the mixer
- The ease of movement and the flow properties of the product

The normalised residence time determines the interval until conditions in the mixer are stationary. In the GCM250, stationary operation occurs after twice the average residence time.

Small but equally efficient

Technically, the small GCM250 with a usable volume of 1 l is every bit as good as the larger GCM mixer. However, it is de-

The design of the mixing chamber and paddles guarantees defined axial and radial mixing



signed for maximum hygienic requirements. The mixing rotor is flying, i.e. it is only mounted at one end with a special, quick-release click connection. The dirty gearbox is separated from the mixing chamber by a second chamber under higher pressure. A pure metal, air-flushed shaft seal ensures that no product enters the gearbox. Ingress is prevented by the special flow design of the dynamic shaft seal. The adjustment of the valve and the filling level in the mixer are observed

through a flush front viewing window. Owing to its small size, the GCM250 micromixer can be integrated into an isolator without difficulty. The mixing chamber, rotor and shaft seal can be removed from the stationary gearbox in a few seconds for cleaning. All processing components can be sterilised in an autoclave.

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