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Selecting the right mixer for the job

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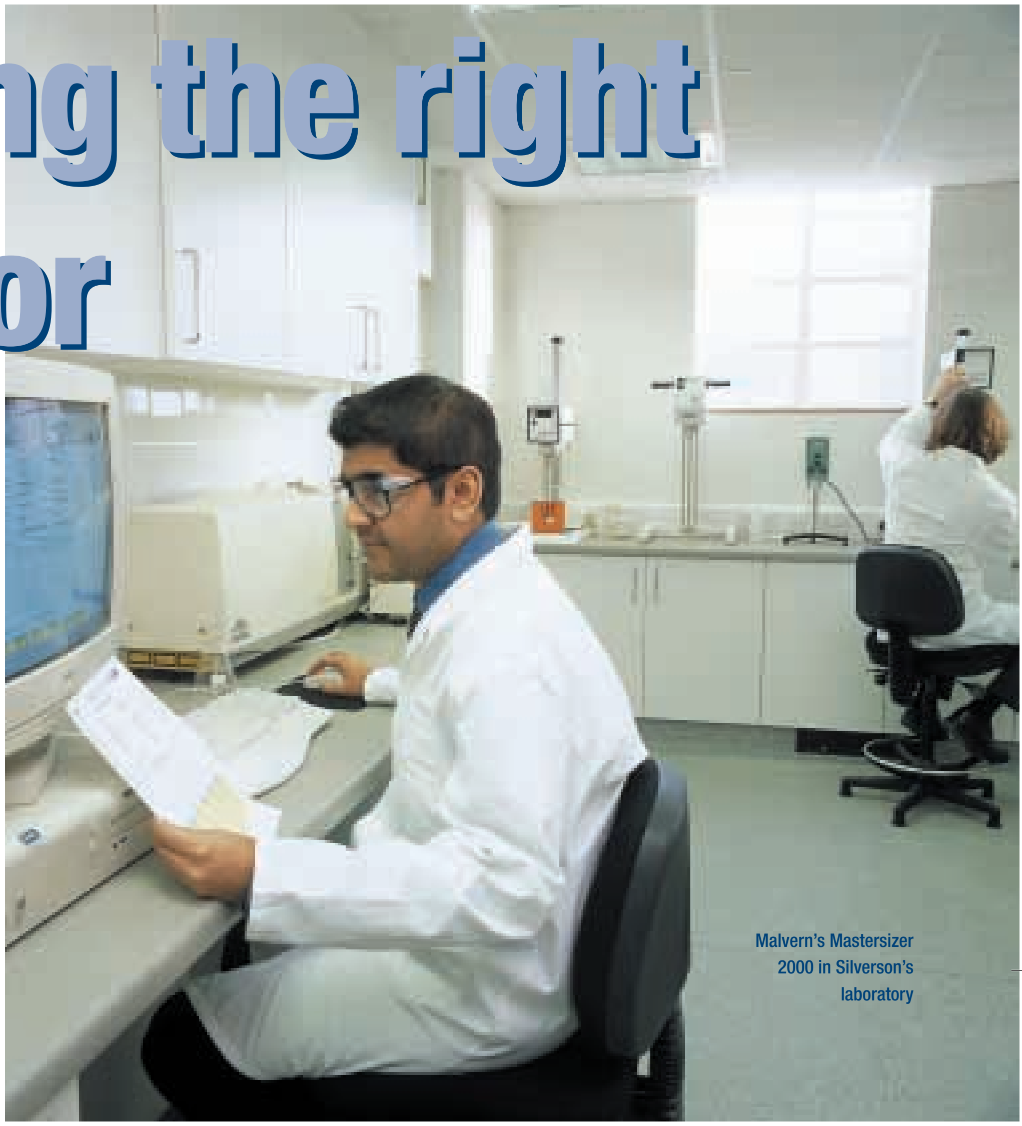


Malvern's Mastersizer 2000 in Silverson's laboratory

Niraj Thapar, of Silverson, and **Paul Kippax**, of Malvern Instruments, report on the approach taken to determine the right mixer for use in processing titanium dioxide pigment used within a tablet coating formulation and how the application of particle size analysis allowed for the specification of the correct mixing technology

Powder dispersion plays a significant role in the manufacture of many pharmaceutical products, with applications ranging from the production of tablet coatings through to the production of parenterals.

Achieving optimum dispersion while maximising process efficiency requires the careful evaluation and selection of appropriate dispersion equipment, both for batch and continuous process applications. It is necessary to strike a balance between the desired product throughput and the degree of dispersion obtained.

With strict controls being applied to the end product properties within the pharmaceutical industry, equipment specification often errs on the side of caution, leading to long processing times. A better understanding of the dispersion process can therefore result in significant benefits in terms of process efficiency. A key parameter in defining the outcome of a given dispersion process is the product particle size.

Particle size is known to be important in defining properties that directly affect pharmaceutical drug delivery, such as solubility rate. However, it is also important in controlling other characteristics such as the hiding power and gloss of the coatings used in tablet production. Here we report on the approach taken to determine the right mixer for use in processing the titanium dioxide pigment used within a tablet coating formulation and how the application of particle size analysis allowed for the specification of the correct mixing technology.

hiding power

A pharmaceutical company needed to prepare a TiO_2 slurry at a concentration of 60% by volume, to be used as the basis of a tablet coating suspension.

The presence of large agglomerates within titanium dioxide dispersions can reduce the pigment hiding power, diminish the gloss of the finished coated surface and yield an ▶

Box 1: titanium dioxide

Titanium dioxide is chemically inert and has exceptional opacity and whiteness. These properties have led to its widespread use in many industries, including pharmaceutical, food and cosmetics manufacture, where it has found application since the 1930s. In the pharmaceutical industry, titanium dioxide is a key component of many tablet coatings. It is also found in cosmetic products such as eyeshadows, oil-based foundations and sunscreens. Foodstuffs containing this versatile chemical include confectionery, icings, and low and no-fat products, of which coffee creamers and salad dressings are just two examples.

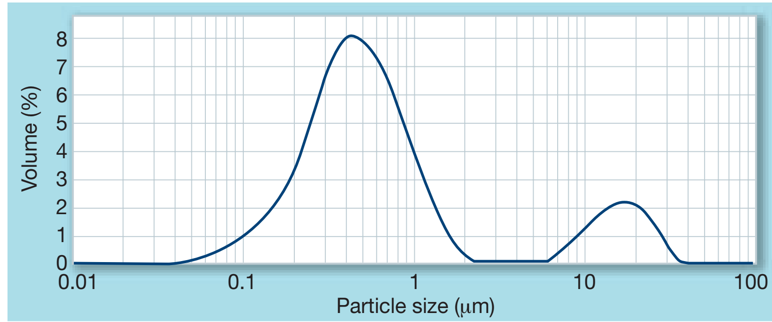


Figure 1 (top right): Particle size distribution of control sample (TiO_2)

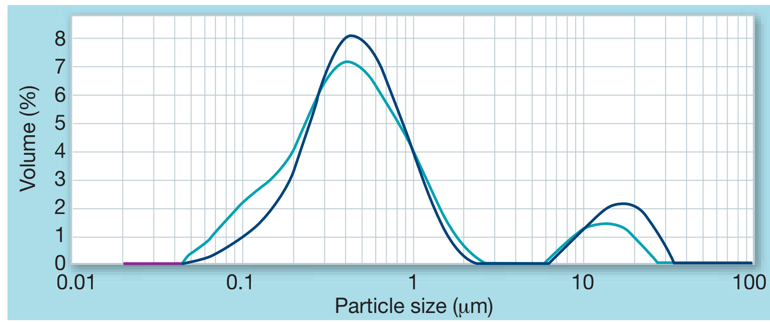
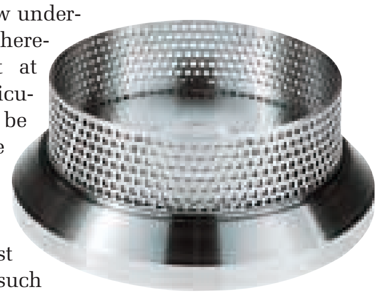


Figure 2 (centre right): control (dark blue) and six minutes (light blue)

Figure 3 (left): GPDH stator and (below) the SQHS stator



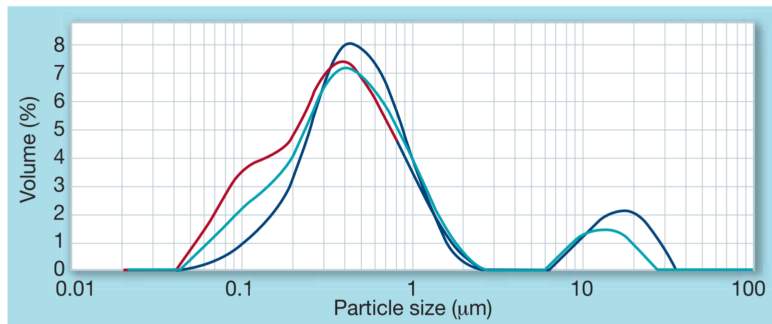


Figure 4 (below right): Control sample (dark blue); six minutes with a GPDH (light blue); and three minutes with a SQHS (red line)

◀ unacceptable yellow undertone. The customer therefore demanded that at least 90% of the particulate material should be less than 1 μm in size in order to deliver the coating film performance.

Selection of the most appropriate mixer for such an application depends on a number of factors, including the batch size (or desired throughput for continuous in-line processes), the formulation type and the viscosity of the end product.

For batches in excess of 1,000 litres an in-line mixer would normally be used and models can vary from standard single-stage units to multi-stage mixers with two, three or even four sets of concentrically mounted rotors and stators.

trial set-up

Trials of mixers and methodologies were conducted at Silverson's pilot plant facility at the company's headquarters in Chesham, utilising the services of the company's on-site laboratory.

Within this facility Silverson can replicate as closely as possible typical manufacturing processes and carry out trials using the customer's own raw materials. Initial trials involved the use of a Silverson 450LS In-Line high-shear mixer. The 450LS unit was installed in a recirculation system with a process vessel fitted with an agitator to disperse the powder and maintain in-tank uniformity.

The particle size distributions observed for different mixing times were measured using the Malvern Mastersizer 2000 installed in the r&d laboratory at Silverson. This system can quantify particulates over a 0.02 – 2000μm range, allowing the detection of both well-dispersed and agglomerated material.

In this instance the customer involved in the trial also used a Mastersizer 2000 for its production quality control testing. Use of the system at Silverson during the mixing trials therefore allowed the titanium dioxide dispersions to be tested and assessed within the tolerances of the customer's own production specification.

Measurements were first made on a pre-mix sample that had not been subjected to high shear. This revealed the presence of large agglomerates of up to 300μm in size as well as smaller particles between 0.04 and 2μm, which were within acceptable limits, figure 1.

Initial trials using a 450LS mixer fitted with a General Purpose Disintegrating Head (GPDH) indicated that the large agglomerates were dispersed to some degree during mixing but that this was only achieved using relatively long mixing times (up to six minutes), figure 2.

In the past, ascertaining that the desired particle size had been achieved would have been much less precise – certainly no assessment to sub-micron level could have been carried out. However, using the Mastersizer 2000 it is possible to understand the performance of the mixing system.

The results at this stage indicated that continued recirculation of the slurry would have no significant impact on the dispersion of the fine particles, even if long residence times were used. This necessitated a change to the mixer geometry.

With rotor/stator type high shear mixers, changes to the stator geometry can allow the throughput and shear rate to be increased or decreased as required, yielding, for example, improved dispersion or shorter mixing residence times. The results presented above were obtained using the GPDH stator. This was changed to a Square Hole High Shear Screen (SQHS) stator, thus altering the mixing characteristics which in turn led to an increase in the applied shear. Figure 3 shows the GPDH and SQHS stators.

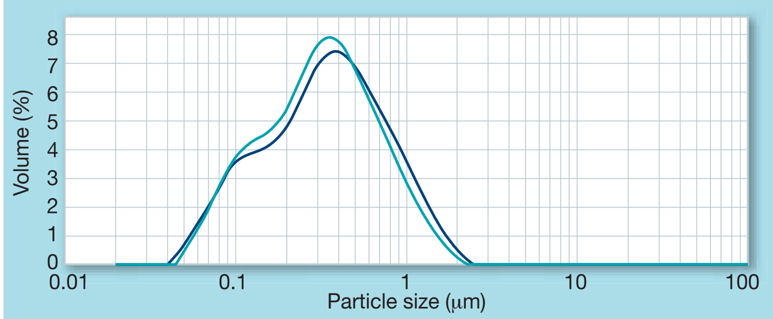
associated advantages

Figure 4 shows the particle size obtained after three minutes' mixing time using the SQHS stator. In this case the large agglomerates had been completely dispersed, while the lower end of the distribution showed a marked size reduction. This illustrates the advantages associated with increasing the shear rate.

The use of the SQHS stator demonstrated that the desired particle size could be achieved within the titanium dioxide dispersion in a relatively short

Figure 5 (left): SLDH head and (below) the multistage in-line mixer

Figure 6 (right): three minutes with a SQHS (dark blue); three minutes with a M/S (light blue)



processing time. Silverson's experience with similar applications suggested that a Multistage In-Line mixer fitted with two concentrically mounted Slotted Disintegrating Heads (SLDH), figure 5, would provide the same or even increased shear rates with the added advantage of greater mechanical strength – especially useful with abrasive products such as titanium dioxide.

Combined with the exceptionally high shear rates generated by a multistage mixing unit, this was expected to provide the best possible configuration for the application. It was therefore concluded that the trial should be redirected at that stage.

Further trials were then carried out using this configuration. The improved results are clearly seen in figure 6 where the particle size produced using

the SLDH unit is shown. Complete agglomerate dispersion was observed along with improved fine particle dispersion. This was achieved within three minutes, thus minimising any potential for wear of the wetted parts of the mixer over time. The customer has since purchased a Multistage unit configured in the same way as the trial machine.

critical choice

Choice and configuration of the correct mixer type is critical if complete dispersion is to be achieved within a given application. Particle size analysis allows users to more fully understand the process of dispersion. In turn, this can enable the performance of different mixer systems to be understood in terms of both dispersion capabilities and the required product throughput, ensuring a robust process solution ■