Production of Nanoparticles Sizes of Active Pharmaceutical Ingredients (API) by Wet Comminution with the DYNO®-MILL

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KEYWORDS

bead milling, DYNO®-MILL, nanoparticle production, comminution

ABSTRACT

The ability to produce nanoparticles by the comminution of suspended solids is improved when using minute ceramic beads with diameters of 0.05-0.10mm in a newly developed bead mill the DYNO®-MILL Model RESEARCH LAB RL. A detailed description of the equipment is included. Example of an inorganic pigment ground at various energy levels and feed rates is presented. Another important example is presented where an Active Pharmaceutical Ingredients (API) had been comminuted in the DYNO®-MILL Model MULTI LAB to a size in the two-digit nanometer range.

INTRODUCTION

Taking full use of small grinding media (beads) of 0.05-0.10mm and the new bead mill DYNO®-MILL Model RESEARCH LAB, experiments were run to demonstrate the ability to produce nanometer sized particles. Whereas larger beads can take up more kinetic energy, which is important for the breakage of particles and true grinding, a packing of smaller beads contains much more beads in the same volume. A high number of beads is especially an advantage for the dispersion of fine particles, where the number of interactions between the particles and the beads play a major role. In stirred media mills, the handling of smaller beads is quite different than in the case of larger beads, because the beads are carried much stronger by the product suspension, which means that the viscosity plays a major role.

EXPERIMENTAL SETUP

The DYNO®-MILL Model RESEARCH LAB (W. A. BACHOFEN AG; GLEN MILLS INC.) that was used for all experiments is shown in Figure 1 and the setup of the grinding chamber is shown in Figure 2. The product enters through a funnel into the inlet and onto the conveying screw (auger), which pumps the product into the grinding chamber, which has a cooling mantle. Since the material is transported by the conveying screw, no external pump is required. The grinding chamber contains the patented DYNO®-Accelerator to throw the beads, which is mounted on the same shaft as the conveying screw. At the outlet of the grinding chamber, a chrome screen is mounted to hold back the grinding beads. If the mill is operated in the circulation mode, the material goes through a steel pipeline and back into the funnel. All grinding beads that were used are made of yttrium stabilized zirconium oxide (specific gravity 6.0).

Figure 1: DYNO®-MILL
Model RESEARCH LAB

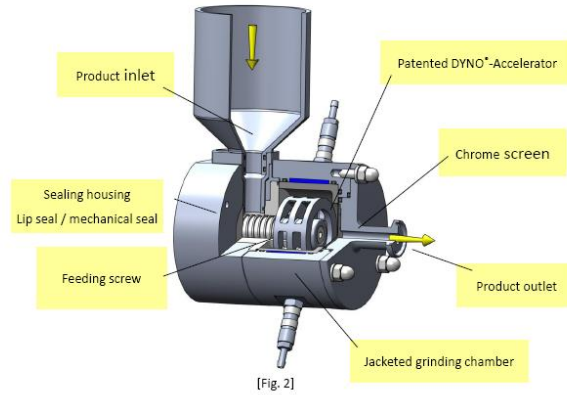

Figure 2: Mill internals showing feed hopper, feed auger, Accelerator®, outlet

BOTTOM-UP or TOP-DOWN

The two ways to produce particles in the nanometer size range are (1) by building up from starting atoms/molecules or (2) by comminution of larger starting particles (Figure 3). All solid materials start with individual atoms or molecules that build up atom by atom, or molecule by molecule, to form a nano-structure. If the size growth process can be arrested at the nanometer scale, the attainment of small particles is achieved.

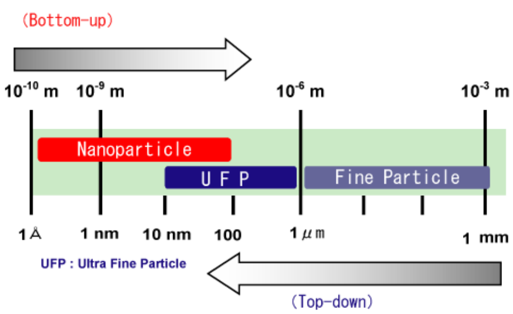

Figure 3: Paths to Nanoparticles

However, in wet processes, such as crystallization and precipitation, or dry processes such as chemical vapour deposition (CVD) the growth may not stop until very large particles are produced. The larger particles, well over tens or hundreds of microns in size, can be either individual large crystals or an agglomeration of minute particles strongly bound together by surface forces.

Producing nanomaterials or structures when starting with a large sized mater will require a high energy comminution technique. This paper describes using such a method, the wet bead milling DYNO®-MILL.

NUMBER OF BEADS vs. DIAMETER

Since the count of beads (grinding media) greatly increases as their diameter decrease, there are more contact points, more collisions, and more active surfaces involved with the comminution. The problem of how to retain such small beads is solved by use of outlet screens with small openings or employing a centrifugal slinger to repel the beads while allowing product to escape the milling zone.

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GRINDING OF AN INORGANIC PIGMENT

A suspension of an inorganic pigment, with a particle size D90 of 5.227 µm, in water was milled with 0.1 mm beads at a filling degree of 65% in the circulation mode. The solid concentration was 30 mass percent. The operating parameters are listed in Table 1.

Time (Minutes)	Agitator Tip Speed (m/sec)	Throughput flow rate (kg/hr)
10	10	7
20	12	7
30	14	6
40	14	5
50	14	5

Table 1: Operating Parameters When Grinding an Organic Pigment

The speed had to be increased, due to a rise in the viscosity. In the end, the minimal shear rate that had to be applied to keep the suspension flowing rose to about 6 Pa, despite the relatively low solid concentration. In the end, however, a particle size D90 of 736 nm was achieved. The frequency curves of the product before grinding (red), after 30 minutes (green), and after 50 minutes (blue) are shown in Figure 8.

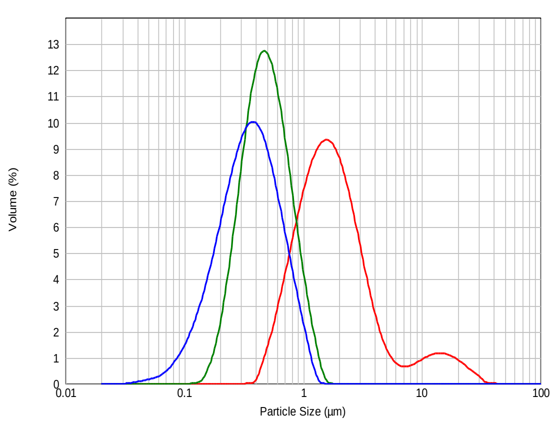

Figure 8: Particle size distribution curves of raw pigment, after 30 minutes, and after 50 minutes

At first the reduction of the particle size is high, because the particles in the range around 10 µm are being "truly grounded". As soon as the particle size is below 1 µm, the dispersion plays a larger role, which can also be seen in the rise of the viscosity. In order to grind further, dispersant would have to be added, because a reduction of the particle size from over 5 µm to less than 1 µm leads to an enormous increase in the solid surface area. Even though no agglomerates were measured, there is practically no difference in the amount of particles in the range above 1 µm between 30 minutes and 50 minutes. It has to be mentioned that 100 nm is at the limit of the measuring range of the instrument. Figure 9 shows the change in the values of D90 over time

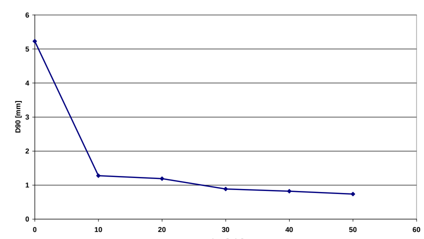

Figure 9: Particle size D90 of an inorganic pigment, as a function of the circulation time

NANOPARTICLES OF API

By employing small diameter beads, long milling times, and high energy inputs, an API that started with D50 of 5.6µ was driven to a D50 of 13nm (Figure 10). Eventually, there was some re-agglomeration to the 100 to 200nm range, but that was acceptable for the pharmacological efficacy was not impeded.

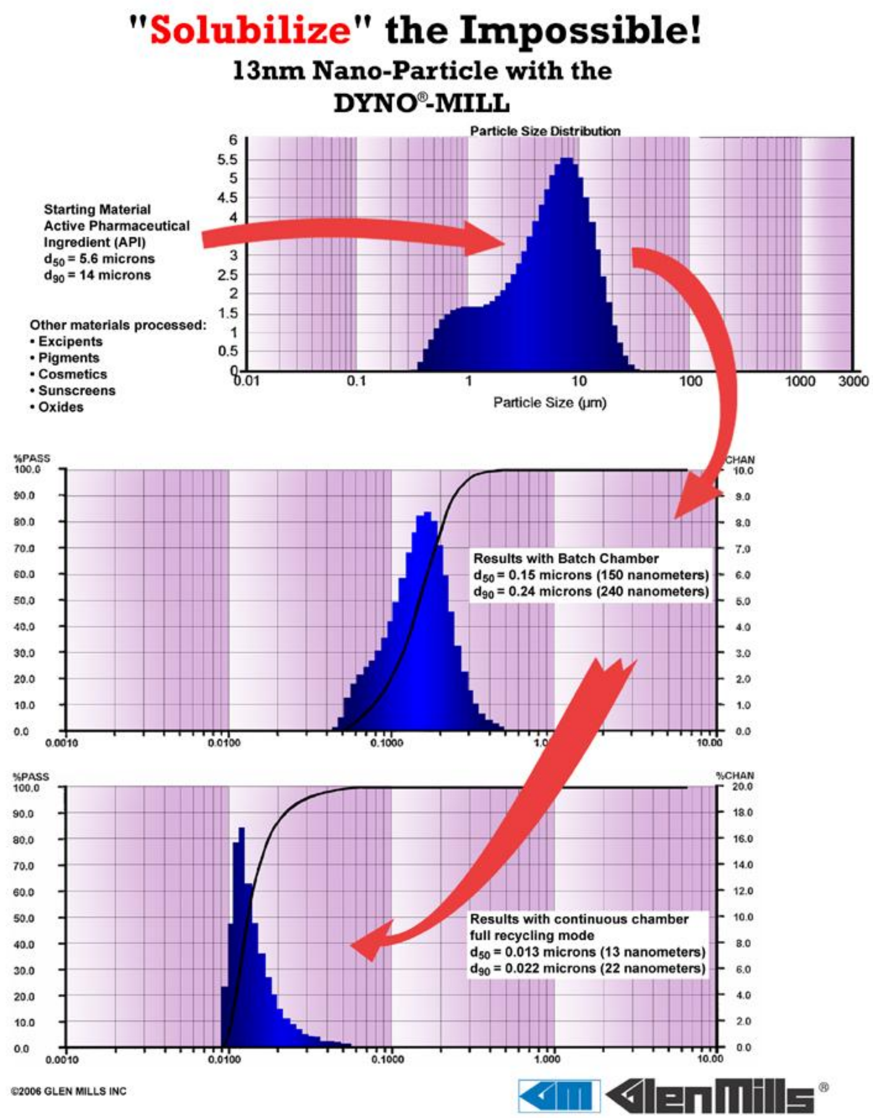

Figure 10: API Comminuted to 13nm with DYNO®-MILL ML

CONCLUSIONS

Using grinding beads with diameters from 0.80mm down to 0.10mm, stable grinding processes can be achieved if one takes into account the higher amount of liquid and dispersant that is required when the particle size is below 1 μm. As with larger beads the addition of more power does not lead to a lower particle size when an optimum has been surpassed. At lower particle sizes, the increased interactions between particles and the liquid lead to a strong increase in the viscosity, and this is especially important if the product is pumped in circulation or more than one pass through the mill. Depending on the product, the viscosity can already increase at solid concentrations of 30 mass percent after a certain grinding time.

Successful comminution of suspended API particles to the nanometer size has been demonstrated. This allows normally insoluble drug compounds to penetrate the cells. The bead mill method (DYNO®-MILL) is demonstrated to be a good platform for this work.