

Micronization and Nanoization of Active Pharmaceutical Ingredients

Stefan Mende

NETZSCH-Feinmahltechnik GmbH, Selb 95100, Germany

Abstract: More than 40% of newly discovered drugs have little or no water solubility which presents a serious challenge to the successful development and commercialization of new drugs in the pharmaceutical industry. Additionally, more than 90% of drugs approved since 1995 have poor solubility, poor permeability, or both. Therefore, it may be necessary to increase the dose of a poorly soluble drug to obtain the required efficacy which can lead to more side effects and higher cost to the patient. Performance of drugs can be improved by decreasing the particle size and, at the same time, increasing specific surface area, dissolution rate and the bioavailability of the drug in the human body. The routes of administration are different and listed as 60% for oral, 5% for pulmonary, 5% for ocular, 5% for topical and 25% for injectable, approximately. The injectable drugs are the most interesting ones for nanoization, because smaller particles will increase performance, and will be useful when using micro needles. In a typical manufacturing process of APIs (active pharmaceutical ingredients) top down processes like high pressure homogenization and wet bead milling are used as standard methods to decrease the particle sizes down to a fineness range of 10 to 500 nanometers.

Key words: APIs, top down process, micronization, bioavailability, scale-up, GMP, reproducibility, IQ, OQ, FAT.

Nomenclature

E [Wh]	Energy
E_{Spec} [kWh/kg]	Mass-related specific energy
P [W]	Power
P_0 [W]	No-load power
m_{Solid} [kg]	Product mass
c_m [-]	Solid mass concentration
\dot{m}_{Susp} [kg/h]	Suspension mass flow
SE_{GM} [Nm]	Stress energy of the grinding media
SN [-]	Number of stress events
ρ_{GM} [kg/m ³]	Grinding bead density
d_{GM} [m]	Grinding bead diameter
v_t [m/s]	Circumferential speed of the agitator

1. Wet Grinding in Agitator Bead Mills

Agitator bead mills belong to a class of grinding machines with freely moving grinding media. The classic examples of this group are the tumbling ball mills known as ball or drum mills. While the power consumption is limited by the critical speed in

tumbling ball mills, the grinding media in agitator mills are set into the relative motion required for grinding by an agitator and are thus provided with the required energy. The grinding chamber is usually stationary. The grinding media charge is set into motion with an agitator.

In continuous operation, the product suspension is pumped into the inlet of the grinding chamber. The agitator is located in the grinding chamber. In general, agitator elements in the form of solid disks, perforated disks, pins or other elements (see Fig. 1) are mounted on a cantilevered shaft. The agitator is run at peripheral speeds of up to 20 m/s. The grinding chamber can be filled with up to 90% bulk volume of grinding media, having a diameter between 0.03 mm and several millimeters. The ground product exits the grinding chamber via a grinding media separation device. This can be, for example, a gap separator or a screen cartridge. In order to cool the product, the grinding chamber usually has a double-walled design.

Corresponding author: Stefan Mende, Dr.-Ing., Manager of Technical and Scientific Communication, research fields: mechanical process engineering, grinding and dispersing processes.

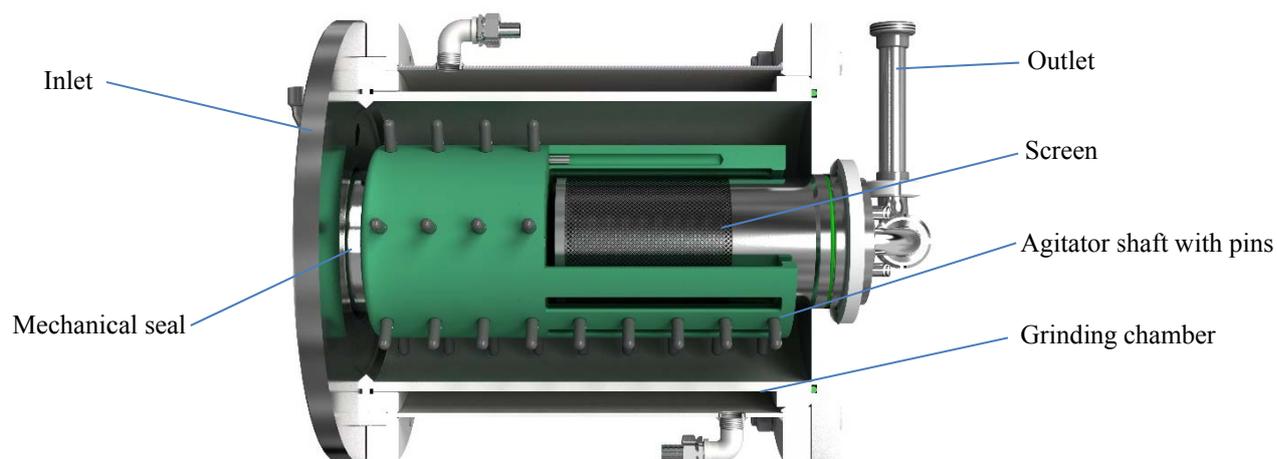


Fig. 1 Schematic draft of a typical peg grinding system used for grinding process of APIs.



Fig. 2 *DELTA VITA*® 600 pilot plant, with cleaning and sterilization in place.

The comminution or deagglomeration of APIs (active pharmaceutical ingredients) is referred to as micronization or nanoization and can bring about various benefits. With the increase in particle surface area associated with comminution, the dissolution rate and thus the bioavailability of the active ingredients can, in part, be drastically increased. This means that the drugs take effect more quickly. Due to the

increased bioavailability, smaller amounts of the API are required which, in turn, leading to a more cost-effective product with fewer risks and side effects for the patient.

NETZSCH machines for comminution and dispersion of pharmaceutical products or those from the life science industries are offered under the name *DELTA VITA*® (see Fig. 2).

In this series, distinction is made between three different levels.

Level 1: Standard machine stand, only parts and components that come into direct contact with the product are pharmaceutical grade

Level 2: Standard design machine stand, parts and components that come into direct and indirect contact with the product are pharmaceutical grade

Level 3: Customized machine design, parts and components that come into direct and indirect contact with the product are pharmaceutical grade

Machines of Level 2 and above are built at the production facility of NETZSCH Premier Technologies LLC in Exton, PA, USA and are shipped with special documentation in the language of the country to which they are delivered. As a rule, these machines are offered with FAT (factory acceptance test), IQ (installation qualification) and OQ (operational qualification). As an option, the customer can receive DQ (design qualification) or a traceability matrix.

Based on extensive experience with the production of machines for the pharmaceutical industry in accordance with the guidelines of GMP (good manufacturing practice), the NETZSCH machines, with sizes ranging from the smallest laboratory scale through to production scale at Level 2 and above, stand out due to the following features:

- All elastomers that come into contact with the product are manufactured and approved according to FDA standards;
- Material, manufacturing and calibration certificates are delivered with the machine;
- CIP (cleaning in place) and SIP (sterilization in place) are available as options;
- All surfaces that come into indirect contact with the product are made of stainless steel or ceramic;
- Data recording and recipe management are available as options;
- User administration with password protection at various levels;

- Laboratory machines can be used with variable grinding chamber sizes;

- Variable grinding chamber designs in ZrO₂, 316 stainless steel or a combination from SiC and Si₃N₄ are available;

- Splash-proof machine stands;
- Comprehensive qualification documents: FAT protocol, IQ, OQ, FS and SDS

- GMP-compliant production of the machines in the USA;

- Training and seminars.

2. Micronization and Nanoization by Wet Bead Milling

The comminution and operational behavior of agitator bead mills was thoroughly researched by Stehr [1] and Weit [2]. A comprehensive factor in the comminution behavior was revealed to be the specific energy, i.e. the energy supplied to the grinding chamber with respect to the mass or volume of the ground product (solid) (see Eq. (1)).

$$E_{Spec}(t_G) = \frac{E(t_Z)}{m_{Solid}} = \frac{P_{Net}}{\dot{m}_{Susp} \cdot c_m} = \frac{\int_0^{t_Z} (P(t) - P_0) dt}{m_{Solid}} \quad (1)$$

Investigations with different sizes of grinding media have shown that, in addition to the specific energy, the grinding bead size has a significant impact on comminution in agitator bead mills (Joost [3], Schwedes [4], Thiel [5], Bunge [6], Mankosa et al. [7], Stadler et al. [8] and Roelofsen [9]). Adjusting the size of the grinding beads to the comminution task yields, to some extent, a significant reduction in the specific energy requirement.

For discontinuous comminution of limestone, Kwade [10] also noted that the circumferential speed of the agitator and the grinding media density had a systematic effect on the correlation between specific energy and product fineness.

As an expression for the kinetic energy of the grinding beads, Kwade [10] defined the stress energy of the grinding media SE_{GM} as a function of grinding

media density ρ_{GM} , grinding bead diameter d_{GM} , and circumferential speed of the agitator v_t (see Eq. (2)).

$$E_{kin} \propto SE_{GM} = d_{GM}^3 \cdot \rho_{GM} \cdot v_t^2 \quad (2)$$

During investigations into the effect of the operating parameters (grinding bead density, circumferential speed of the agitator disk and grinding media size) he was able to show that with constant specific energy input, there was an optimal stress energy at which the greatest product fineness could be achieved.

3. Optimization of Grinding Parameters

These effects should become clear through a simple example for an API named Flubendazole.

Tests were carried out with a *DELTA VITA*[®] 600 Pilot plant machine together with a customer. The *DELTA VITA*[®] 600 is a machine with a grinding chamber volume of app. 600 mL, and is suitable for suggested batch size between 1 and 6 liters.

For this discussion the original data from trails with customers are modified slightly in all pictures because of nondisclosure agreements! But, qualitatively, the results show the right correlations and influences of the discussed operating parameters.

For the determination of an optimum value, a minimum of three test settings are required. The range of optimal stress energy required to advance the comminution is not always attained. With regard to operational reliability or the target product throughput, in many cases it appears to be impractical to use even smaller grinding beads.

In this example, a solid form of Flubendazole with an initial particle size of $d_{10} = 1.54 \mu\text{m}$; $d_{50} = 4.47 \mu\text{m}$ and $d_{90} = 13.2 \mu\text{m}$ was processed with identical grinding beads having a diameter of 0.3 mm in the same mill in recirculation mode operation and with three different circumferential speeds of the agitator shaft of 6 m/s, 10 m/s and 12.3 m/s.

The desired particle size distribution was determined during the drug development process as

$d_{10} = 0.03 \mu\text{m}$; $d_{50} = 0.167 \mu\text{m}$ and $d_{90} = 0.7 \mu\text{m}$.

After different grinding times, samples were taken at the outlet of the mill and analyzed with a Malvern MasterSizer 3000.

The results of the test are shown in Fig. 3, where particle size is a function of specific energy input. The target particle size distribution was achieved with 6 m/s agitator speed, and with a specific energy input of 0.403 kWh/kg_{Solid}. To achieve the same particle size distribution with an agitator speed of 10 m/s, a higher specific energy input of 0.569 kWh/kg_{Solid} was required. Whereas with 12.3 m/s agitator speed, the particle size distribution could not be achieved because of any effect. This demonstrates that, with the grinding media used, the desired target value can be achieved with the lowest circumferential speed of the agitator shaft and the lowest specific energy consumption. However, due to the very low power input at these settings, the resulting production capacity is also the lowest.

This finding is confirmed when one now considers the stress energies of the grinding media for the tests conducted (see Fig. 4). Now, the goal is to achieve the highest production capacity with the lowest energy requirement. To this end, the stirrer tip speed of the agitator shaft is increased and the grinding media size is calculated for which the same stress energy per grinding bead impact is available (reference the following calculation).

Because of the fact that with an agitator speed of 12.3 m/s the temperature limit of the product of 35 °C was exceeded and the desired particle size distribution could not be achieved, an agitator speed of 10 m/s was chosen for that calculation.

$$\begin{aligned} SE_{GM,A} &= SE_{GM,D} \\ d_{GM,A}^3 \cdot \rho_{GM,A} \cdot v_{t,A}^2 &= d_{GM,D}^3 \cdot \rho_{GM,D} \cdot v_{t,D}^2 \\ \rho_{GM,A} &= \rho_{GM,D} \\ v_{t,A} &< v_{t,D} \\ d_{GM,D} &= d_{GM,A} \cdot \sqrt[3]{\frac{v_{t,A}^2}{v_{t,D}^2}} \\ d_{GM,D} &= 0.3 \cdot \sqrt[3]{\frac{6^2}{10^2}} = 0.253 \text{ mm} \end{aligned}$$

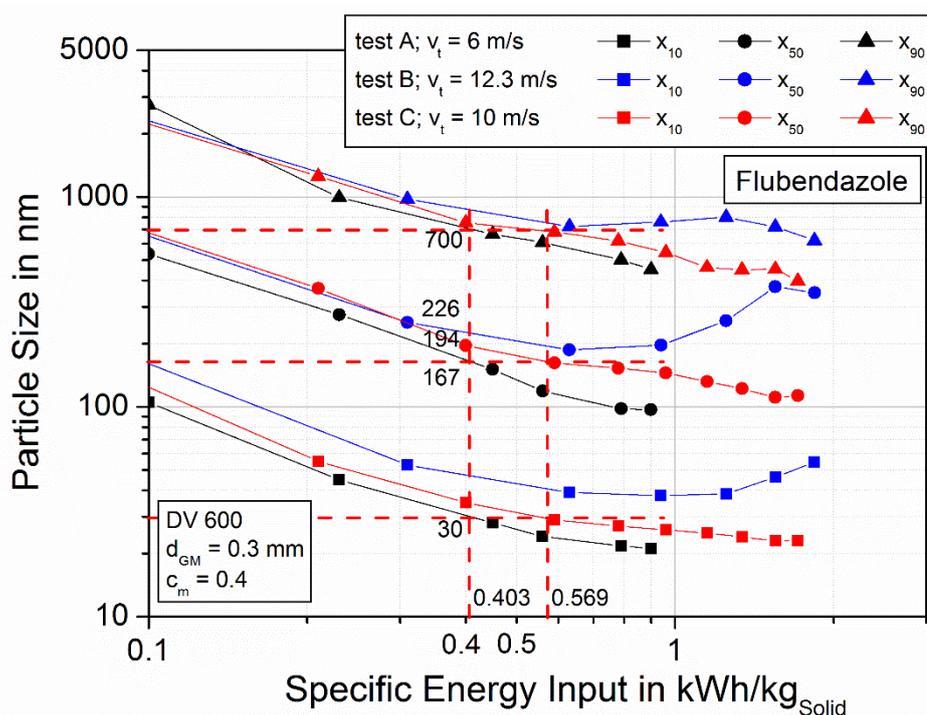


Fig. 3 Comminution of Flubendazole with different circumferential speeds of the agitator shaft.

Table 1 Calculation of stress energies of the grinding media and comparison of grinding results for constant specific energy.

Test	d_{GM} mm	v_t m/s	P_{Net} kW	ρ_{GM} kg/m ³	d_{50} nm	Temperature °C	SE_{GM} kgm ² /s ²
A	0.3	6.0	0.21	6,050	167	21	5.881E-06
C	0.3	10.0	0.62	6,050	226	27	1.634E-05
B	0.3	12.3	0.98	6,050	194	36	2.471E-05
D	0.2	11.0	0.74	6,050	167	30	5.856E-06

Now, a grinding media size of 0.25 mm is not available. So, grinding media of a diameter of 0.2 mm should be used. Therefore the necessary agitator speed

has to be calculated for which an equal stress energy per grinding bead impact is available.

$$SE_{GM,A} = d_{GM,A}^3 \cdot \rho_{GM,A} \cdot v_{t,A}^2 = d_{GM,D}^3 \cdot \rho_{GM,D} \cdot v_{t,D}^2$$

$$v_{t,D} = \sqrt{\frac{SE_{GM,A}}{d_{GM,A}^3 \cdot \rho_{GM,A}}} = \sqrt{\frac{5.881 \cdot 10^{-6} \cdot 10^9}{0.2^3 \cdot 6050}} = 11.02 \text{ m/s}$$

If grinding beads with a diameter of 0.2 mm, rather than 0.3 mm, are used with a constant grinding media density and circumferential agitator shaft speeds of 11 m/s, the comminution results are comparable when plotted as a function of specific energy (see Fig. 5).

Considering the possible production rates, it becomes clear that a higher production capacity can be achieved merely by increasing the power input due to

the increase in the tip speed of the agitator shaft, and thus the kinetic energy of the grinding media. However, this higher production capacity is associated with an increased specific energy requirement.

In contrast, with simultaneous optimization of the grinding bead size, the production capacity can be increased tremendously without the necessity of higher energy inputs.

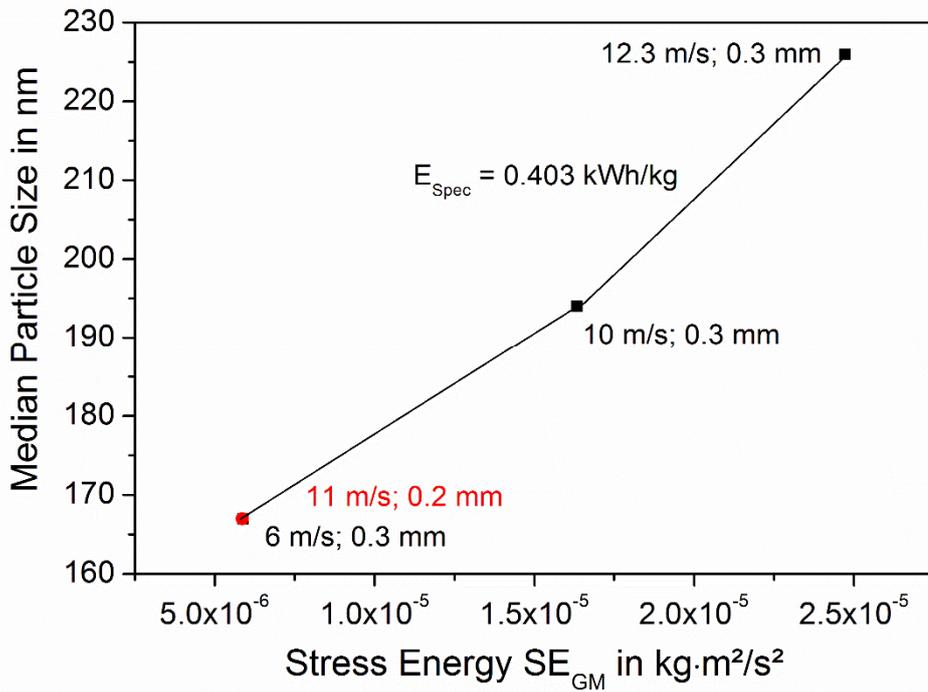


Fig. 4 Comminution results as a function of the stress energy of the grinding beads.

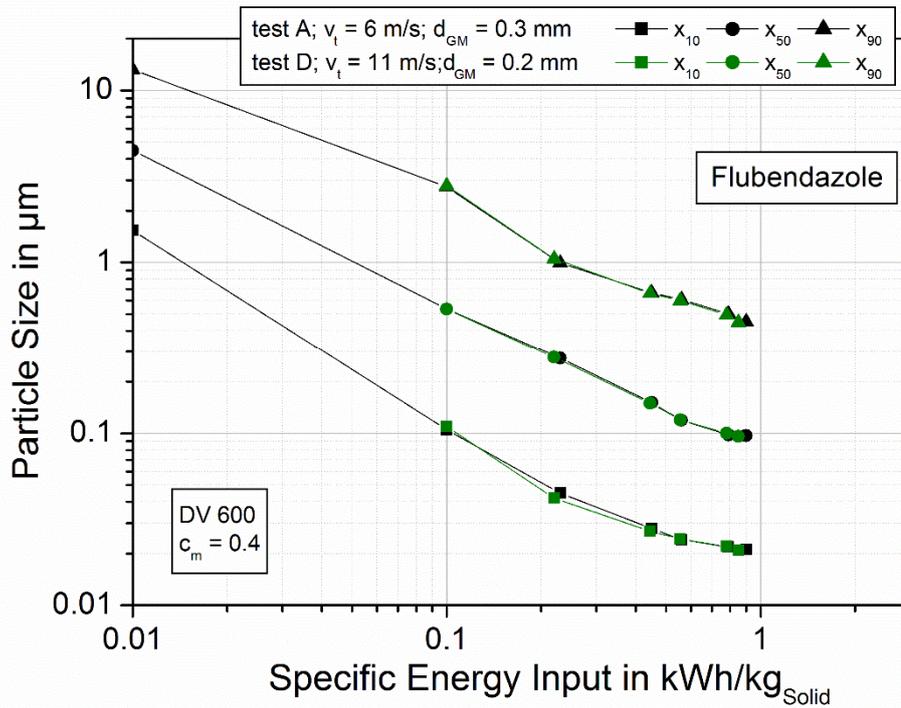


Fig. 5 Comminution of Flubendazole with different agitator shaft speeds, and different bead sizes.

$$\dot{m}_{\text{Production}} = \frac{P_{\text{Net}}}{E_{\text{Spec}}}$$

$$\dot{m}_{\text{Production,A}} = \frac{0.21 \text{ kW} \cdot \text{kg}}{0.403 \text{ kWh}} = 0.52 \frac{\text{kg}}{\text{h}}; \quad 6 \text{ m/s and } 0.3 \text{ mm beads}$$

$$\dot{m}_{\text{Production,C}} = \frac{0.62 \text{ kW} \cdot \text{kg}}{0.569 \text{ kWh}} = 1.09 \frac{\text{kg}}{\text{h}}; \quad 10 \text{ m/s and } 0.3 \text{ mm beads}$$

$$\dot{m}_{\text{Production,D}} = \frac{0.74 \text{ kW} \cdot \text{kg}}{0.403 \text{ kWh}} = 1.84 \frac{\text{kg}}{\text{h}}; \quad 11 \text{ m/s and } 0.2 \text{ mm beads}$$

That means, even with an higher power input to the machine just by the use of smaller grinding media of 0.2 mm, instead of 0.3 mm, and a slightly higher agitator speed of 11 m/s, instead of 10 m/s, an app. 75% increased capacity of the production process obtained. A product with constant quality can be produced without higher specific energy requirement and therefore without an increase of wear of the machine parts or the grinding beads as well as without an increase of the contamination of the high quality product.

4. Scalability

A customer developed, tested and approved a commercial API with a fixed particle size distribution with a $d_{99} < 400 \text{ nm}$ (see Fig. 6). A scale-up from the pilot phase to the real production size became necessary.

Once the operating parameters have been optimized, the results have to be transferred to production-size mills. For this scale-up process two essential roles have to be followed:

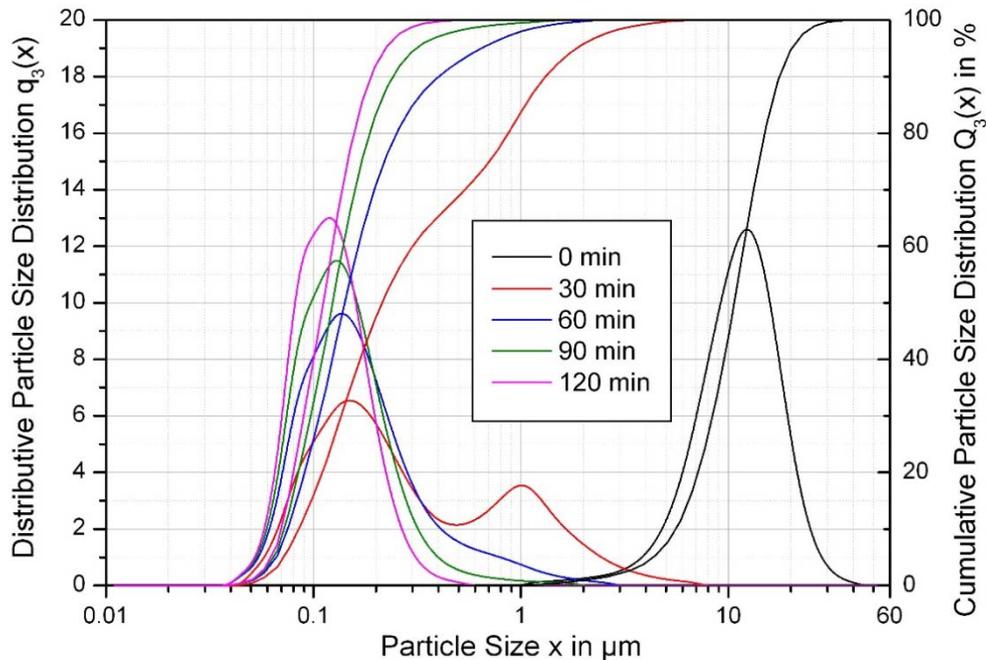


Fig. 6 Development of the particle size distribution obtained during a grinding in a DELTAVITA® 600 pilot plant.

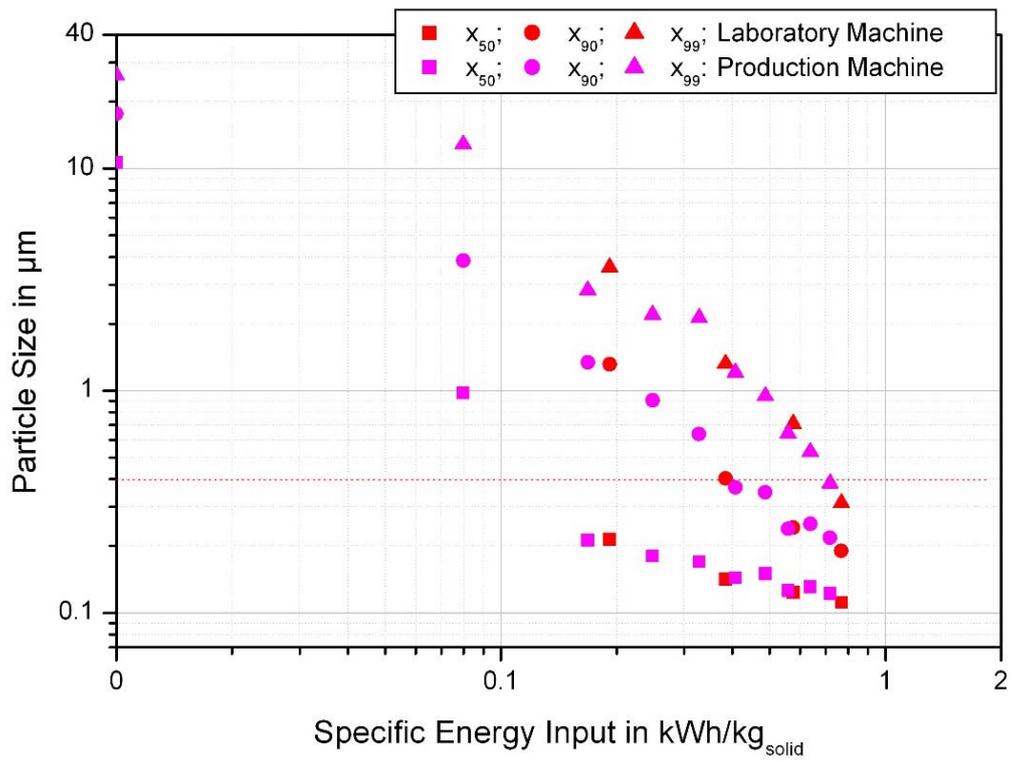


Fig. 7 Results of the scale-up from a pilot agitator bead mill to a production-size mill.



Fig. 8 DELTAVITA[®] 60 000 with special design for wall installation.

(1) It has to be guaranteed that the product suspension would not exceed a defined maximum temperature during the comminution process.

(2) The exact same particle size distribution has to be achieved and reproducible with the same technology at the same specific energy input with the similar operating parameters.

The essential parameter for the scale-up is the specific energy input. Fig. 7 shows the results of the scale-up from a *DELTA VITA*[®] 600 pilot agitator bead mill to a production-size mill *DELTA VITA*[®] 60 000 (see Fig. 8).

The illustration clearly shows that the results of the pilot plant can be exactly transferred to the production-size plant.

5. Summary

The optimization of wet grinding processes offers tremendous potential for energy savings, increase of production capacities, and improvement of product qualities. The theoretical background is well known, published and approved in the practice.

An exact reproducible scale-up of micronization and nanoization from the laboratory scale to the real production scale is possible.

References

- [1] Stehr, N. 1982. "Zerkleinerung und Materialtransport in einer Rührwerkskugelmühle (Grinding and Material Transport in Agitator Bead Mills)." Dissertation, TU Braunschweig.
- [2] Weit, H. 1987. "Betriebsverhalten und Maßstabsvergrößerung von Rührwerkskugelmühlen (Operational Performance and Scale up of Agitator Bead Mills)." Dissertation, TU Braunschweig.
- [3] Joost, B., and Kwade, A. 1996. "Feinstzerkleinerung in Rührwerksmühlen. (Fine Grinding in Agitator Bead Mills)." *Das Keramiker-Jahrbuch*.
- [4] Schwedes, J., and Kwade, A. 2009. "Basic Course Grinding and Dispersing with Stirred Media Mills." Institute for Particle Technology, TU Braunschweig.
- [5] Thiel, J.-P. 1993. "Energiebedarf und Durchsatzverhalten der Kohlenasszerkleinerung in einer Rührwerkskugelmühle (Energy Demand and Troughput Behavior for Wet Grinding of Coal in Agitator Bead Mills)." Dissertation, TU Braunschweig.
- [6] Bunge, F. 1992. "Mechanischer Zellaufschluß in Rührwerkskugelmühlen (Mechanical Disintegration of Micro-organisms in Agitator Bead Mills)." Dissertation, TU Braunschweig.
- [7] Mankosa, M. J., Adel, G. T., and Yoon, R. H. 1986. "Effect of Media Size in Stirred Ball Mill Grinding of Coal." *Powder Technology* 49: S. 75-82.
- [8] Stadler, R. Polke, R., Schwedes, J., and Vock, F. 1990. "Naßmahlung in Rührwerkskugelmühlen (Wet Grinding in Agitator Bead Mills)." *Chemie-Ingenieur-Technik* 62: 907-15.
- [9] Roelofsen, D. P. 1991. "Entwicklungen auf dem Gebiet des Pigmentdispargierens mit Rührwerkskugelmühlen (Developments on the Field of Dispersing of Pigments with Agitator Bead Mills)." *Farbe + Lack* 97 (3): S. 235-42.
- [10] Kwade, A. 1996. "Autogenzerkleinerung von Kalkstein in Rührwerksmühlen (Autogeneous Grinding of Calcium Carbonate in Agitator Bead Mills)." Dissertation, TU Braunschweig, ISBN 3-8265-2082-3.