INVESITGATION OF A SUB-MICRON MILLING PROCESS OF POORLY WATER SOLUBLE PRODUCTS USING FACTORIAL DESIGN.

S.L.A. Hennart[1,2], M.C. Domingues[3], W.J. Wildeboer[1] and G.M.H. Meesters[1,2]

1. DSM Food Specialties, R&D Recovery and Formulation, Delft, THE NETHERLANDS
2. Delft University of Technology, Nano Structured Material Group, Delft, THE NETHERLANDS.
3. University of Coimbra, Faculty of Sciences and Technology, Coimbra, PORTUGAL.

Abstract – The objective of this work was to investigate the mechanisms of very fine grinding in a wet ball milling set-up as a function of the product properties and process parameters. The ball mill used was a Dynomill and the grinding media consisted of zirconium oxide beads. The grinded powder was a poorly water-soluble product. Laser diffraction techniques were used to analyze the particle size distributions.

During grinding the average particle diameter of a particulate product is reduced to a minimum size. The grinding experiments showed that for a specific product this minimum size is a fixed constant within the range of tested operating conditions.

The grinding parameters (rotation speed of the mill, the grinding media size) are being further investigated to be able to control the grinding process (and optimize the grinding time) and to reach the desired particle attributes (minimizing size).

The grinding time was strongly dependent on the grinding media size and on the rotation speed in a second order of importance. The grinding process becomes faster when the rotation speed increases and the grinding media decreases.

1. INTRODUCTION

Poorly water soluble products are challenging for formulation scientists. The impossibility to dissolve compounds in water based matrixes requires innovative research for the optimization of the application of the product. In the field of pharmaceuticals for example, target release and bio availability are strongly affected by the solubility properties (solubility and solubilisation rate) of the product. One way to increase the efficiency of the product is often to tune the particle size distribution of the powder material. Decreasing the particle size increases the surface area and thus increases the availability of the product.

High shear wet ball milling enables to reach extra fine particle sizes and thus to improve the product efficiency[1]. In order to be capable to reach desired particle size distributions, the grinding process needs to be well understood. Not only the particle size, the time of grinding is an important variable as well.

A grinding process in a ball mill can be influenced by several parameters. Molls, H.H. and Hornle, R. described 44 of them[2]. Even if not all parameters have the same degree of importance, and some of them could be considered as not influent; the complexity of the system is evident. The focus in this research was to study the more important parameters: the rotation speed of the stirrers and the grinding media size. All other possible parameters (flows, charge of the grinding chamber, concentration of product, etc) are kept constant. The present work aims to understand the importance of those main parameters in order to optimize the milling process and reach the product specifications in terms of particle size and time of grinding.

A factorial design allows the simultaneous analysis of the effect of the parameters as independent variables and their degree of interaction. This tool is especially efficient for complex system with multiple variables and responses, such as ball mills. The statistical computation by software enables to get with a restricted number of experiments a quantitative overview of the different process parameters studied. In the present study, the variables are the rotation speed of the stirrer in the mill, the grinding media size. The response variables is the time of grinding.

2. EXPERIMENTAL WORK DICTED BY FACTORIAL DESIGN

2.1. Grinding process

The grinding has been performed on a ball mill (Dynomill, Bachofen AG, Switzerland). Particle size distributions have been measured with a laser diffraction size analyzer (LS230 equipment from Beckman Coulter).

The ball mill was operated in a recirculation mode. Figure 1 shows how the suspension of product is pumped in the grinding chamber which is filled with a grinding media and how the product is drawn out through a filter preventing the grinding media to exit the milling chamber. The system is cooled to keep constant controlled temperature in the entire system.

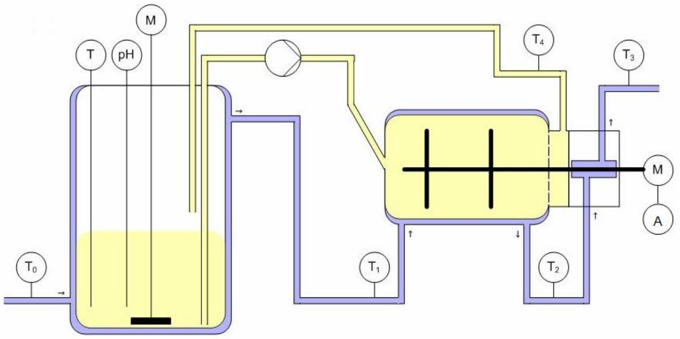

Figure 1 . Grinding set-up and controls, where T is a temperature measurement and pH is a pH control point.

The particle size distributions of the samples taken from the stirred vessel were measured at different times during grinding. Figure 2 is an example of the data obtained from the experimental work.

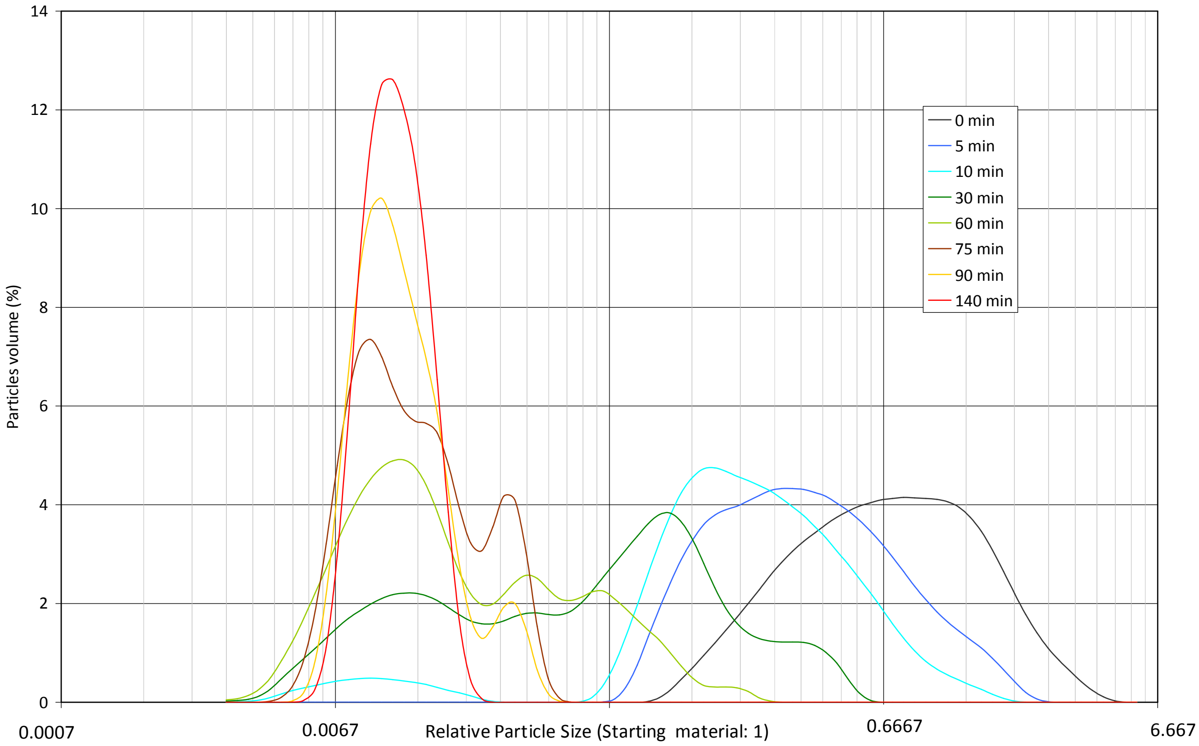

Figure 2 . Evolution of the particle size distribution at different grinding times.

2.2. The factorial design.

In the following study, the number of level for the different parameters is chosen:

The rotation speed is studied at 2 levels: the maximum and the minimum of the operating range: 2000rpm and 6000rpm.

The grinding media size is studied at three levels: 0.3, 0.5 and 0.8mm beads are tested. In the study of the contamination, a 2-level factorial design is drawn using 0.3 and 0.8mm beads.

The factorial design software used, Statraphics Plus 5.1 (StatPoint, Inc), defines a work plan to produce the required output data.

The objectives are to determine the influence of the rotation speed and the grinding media on the required time of grinding to reach a given particle size. Several response variables are therefore created: the time to reach a product particle size of 5µm, 2µm, 1µm, 0.5µm and 0.2µm.

For each response variable, the statistical program runs an analysis of variance giving the effect of each process parameter (grinding media and rotation speed) on the studied response.

3. COMPUTATION OF EXPERIMENTAL RESUTLS

3.1. The effect of individual parameters and of combined parameters on the time of grinding

To analyze the effect of the parameters on the time of grinding, factorial design are carried out for different product particle sizes. The calculations are done according to the method used by Statgraphics 5.1 software called ANOVA (ANalysis Of VAriance). The effect of the parameters is measured as the average response at the high level of the factor minus the average of the response at the low level of the factor. Therefore, the higher the effect, the more influence the parameter has. As shown in Figure 3 the pure effect of the parameters is increasing exponentially when considering smaller particle sizes. Thus the influence of the parameters is very strong on the time of grinding, especially when extra fine particle size as sub-micron particles are desired.

The effect of the parameters rotation speed and the combination rotation speed and grinding media size is negative. Thus, the higher the parameter, the less grinding time is required. Opposite to this the grinding media size has a positive effect on the time: the smaller the grinding media, the less time is required.

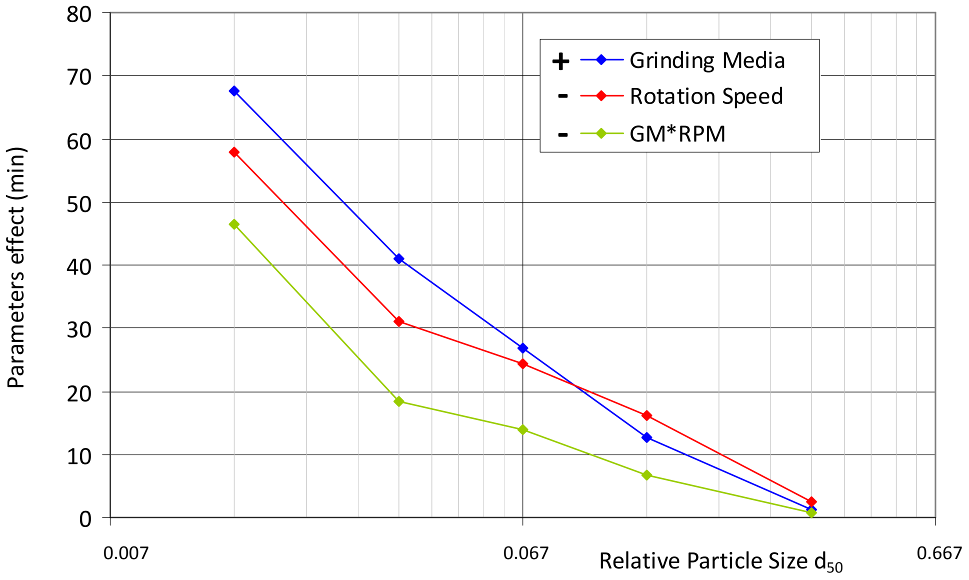

Figure 3 . Parameters effect on the time of grinding to reach different product d_{50} particle size.

In previous studies using population balances to model the ball milling process (to be published[3]), the time of grinding has been defined as function of the process parameters.

The time required to reach 100.P percent of particles below a given size x_i is a function of the initial quantity of particles ($R_i°$) above x_i and the selection function Q_i. (Eq. 1)

$$t(P\% < x_i) = \frac{-1}{Q_i} \cdot \ln\left(\frac{1-P}{R_i^0}\right) \qquad (1)$$

In the factorial design, the target particle sizes are below the initial particle size distribution of the product particles, therefore, $R_i°$ equals 1. The target particle sizes are median sizes (d_{50}) and P equals 0.5.

According to the model developed and validated, the expression of the grinding time is thus as in Eq. 2.

$$t(50\% < x_i) = \frac{0.69 \cdot d_{GM}}{v_{tip} \cdot x_i^{d_{GM}^3 \cdot v_{tip}^2}} \quad (2)$$

The trends are equal: The bigger the grinding media, and the slower the rotation speed, the longer the grinding time. The time is a function of the inverse of the particle size, but the effect of the parameters are defined as the difference between the average between the maximum and the minimum value of the parameters and thus this difference will increase with time. To look at the real changes in the effect of the parameters and to be able to compare the parameters to each other, the sum of the effects needs to be normalized.

In order to be able to compare the relative effect of different parameters versus the particle size, the effect have been standardize to 100%. Thus the value of the relative effect represents the contribution of the studied parameter to the grinding time for a desired particle size. Graphs are represented in Figure 4. The rotation speed is the most important parameter for the grinding of coarse particles. To reach sub micron particles, the grinding media is the dominant factor.

In a previous study (Hennart et al.[4]) the grinding mechanism in the same stirred ball mill for the same product was determined. Coarse particles mainly undergo cleavage and the production of extra fine particles is resulting from an abrasion mechanism. The importance of the grinding parameters on the time of grinding is resulting of an influence of the parameters themselves on the grinding mechanism.

Cleavage occurs by the application of low and high forces such as compaction in the centrifuge bed of grinding media. Thus grinding media as individual particles are not relevant, but much more the loading of media in the grinding chamber is key. The loading is kept constant in the series of experiment. In the case of cleavage, the intensity of the applied forces and therefore the speed of centrifugation is much more important than the number of contact and thus the grinding media size.

Abrasion is a result of tangential forces applied on the mother particle. Typically those forces are also present in the centrifuge bed of grinding media. The speed and the energy of the impact is then less important than the number of the potential impact. The number of those impacts depends on the number of grinding media particles that are present in the mill and is at constant load ratio, the number of grinding media particles is increasing when decreasing the media size.

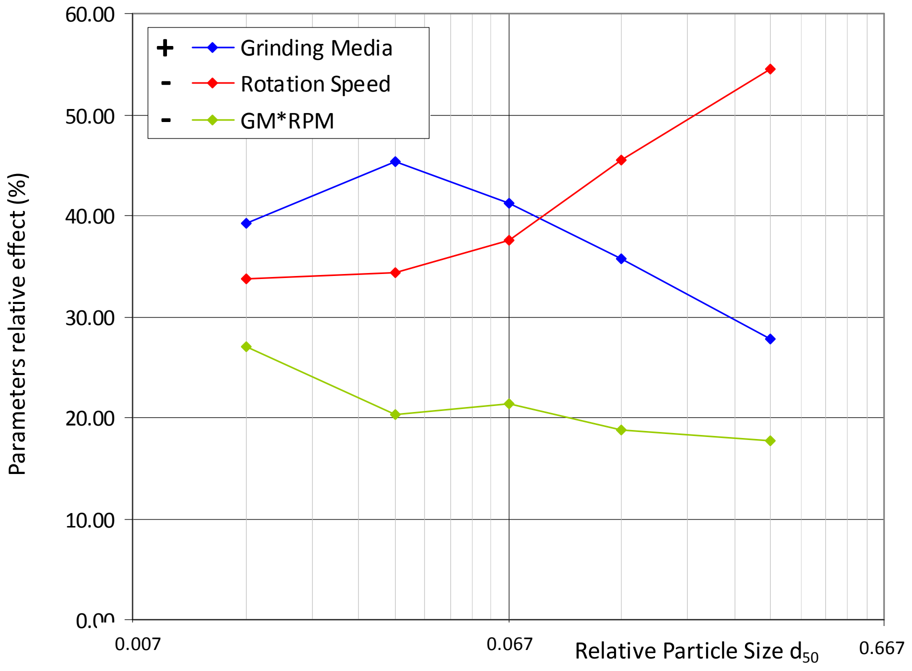

Figure 4 . Relative effect of the different parameters and combination of parameters on the time of grinding to reach different particle sizes.

By taking into consideration the grinding mechanism, it is then clear that the effect of the grinding media size and the rotation speed calculated (Figure 4) is dependent on the size of the particles being broken. The grinding media size is more relevant than the rotation speed in the case of production of fine particles. The number of impacts determined by the number of grinding media particles is dominant. And in case of coarse particles the breakage is initiated by high centrifuge forces of compression in the packed bed of grinding media particles, thus explaining that the rotation speed is a dominant factor.

4. CONCLUSION

The use of a factorial design to determine the effect of the principle process parameters brings the following conclusion:

In the studied wet stirred ball milling process, the grinding media size is the most important factor with regard to the time of grinding. The smaller the grinding media, the quicker the grinding takes place. Higher rotation speed enables as well shorter grinding time.

Optimization of the mill would therefore mean, firstly a reduction of the grinding media size, thus lowering the grinding time. Secondly, faster grinding can be obtained by increasing the rotation speed.

5. NOMENCLATURE

P	: Percentage, dimensionless
X_i	: Product particle size class, µm
t	: Time, min
Q_i	: Selectivity function from the model, dimensionless
R_i°	: Initial cumulative weight fraction, dimensionless
d_{GM}	: Diameter of the grinding media, mm
v_{tip}	: Tip speed, rpm or m/s
GM	: Grinding media
RPM	: Rotation speed

6. REFERENCES

---

[1] E. Merisko-Liversidge, G.G. Liversidge, E.R. Cooper; Nanosizing: a formulation approach for poorly-water-soluble compounds; *European Journal of Pharmaceutical Sciences*; **2003**; 18; 113-120.

[2] Molls, H.H. and Hornle, R.; DECHEMA; **1972**; Monography 69 Tl 2; 631-661.

[3] S.L.A. Hennart, V. Drouet, W.J. Wildeboer and G.M.H. Meesters; Modeling of Sub-Micron Milling Processes Limited by re-Agglomeration Phenomena; To be submitted.

[4] S.L.A. Hennart, W.J. Wildeboer and G.M.H. Meesters; Identification of The Grinding Mechanisms and Their Origin in a Stirred Ball Mill Using Population Balances; To be submitted.