Optimization of a Grinding and Dispersal Equipment for Active Pharmaceutical Ingredients using CFD

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Abstract: This paper presents the design optimization procedure of a wet bead mill for active pharmaceutical ingredients by highly efficient numerical and experimental methods. In a first step, computational fluid dynamics (CFD) simulations, calibrated and validated by particle image velocimetry (PIV) measurements on the machine, allowed to obtain useful and reliable insight on the characterization of the three-dimensional flow inside the mill. This enabled the optimization of specific elements such as the stator or rotor stage geometry inside the mill. Furthermore, a ceramic prototype of the rotor was produced while respecting manufacturing and contamination constraints; it demonstrated experimentally that the efficiency of milling had been improved. In a second stage, the simulations focused on the filter-free separation of the beads from the ground material suspension. The separation process was optimized numerically until obtaining a result of 100% separation. The interaction between the separation simulations and empirical tests was carried out in a particularly productive manner thanks to the fast prototyping of the separator elements using 3D printing, which confirmed the excellent quality of the separation.

Keywords: Milling; PIV; CFD; geometry optimization

1. Introduction

A major trend in the pharmaceutical industry is "targeted drug delivery", the main advantages of which are the ability to handle sick cells only and so to limit side effects, at the same time reducing as well the amount of medicine needed and therefore the price of treatment [2]. One of the basic principles of “targeted drug delivery" is to increase the reactivity of the drug particles by decreasing their size, their specific surface thus becoming greater (Brunauer-Emmet-Teller (BET) theory). Crystals of active ingredients are hard to grind – they collectively have a hardness comparable to that of marble – and their size is usually of the order of several hundred microns. The equipment described in this project originally allowed a reduction of the size of these particles to approximately 100 nanometers. With certain improvements, even smaller particle sizes could be achieved, but the phenomenon of self-aggregation prevents an effective grinding of dry powders below the size of one micrometer. Therefore, manufacturing of nanometric particles by a grinding process (top-down) and the dispersion of agglomerated particles must be realized in a liquid environment, i.e., in suspensions containing the active ingredient particles, solvents and diverse additives and surfactants allowing to keep the particles distant from one another. Additionally, it has the advantage of limiting active ingredient losses since dust explosion is prevented. In order to effectively reduce the size of particles, grinding media – for example beads of ceramic ZrO2 – are also added to the process; it is in fact the shocks between these beads which break the particles of active ingredient.

This method, called wet bead milling, has become state of the art for Frewitt Ltd., a company active in the development of fine milling processes for various sectors of the industry. Willing to offer products of high quality and to address future needs of its customers, Frewitt SA. strives for innovation and for the optimization of its products. It is in this spirit that the company mandated the University of Applied Sciences of Western Switzerland in Fribourg to conduct a cutting-edge mill optimization project.

The purpose of this project is to study the unsteady three-dimensional turbulent flow inside an existing wet bead mill and to optimize the design of the equipment by numerical methods and continuous experimental validation. Actually, the project goals can be divided into 2 categories: technical and scientific objectives. The technical objective is the measurement of the instantaneous speed and pressure fields. These measurements are necessary for the experimental characterization of the flow inside the mill with a high precision, in order to validate first the simulation and then the newly developed design. The characterization of the flow inside the mill in numerical simulations represents the scientific objective.

This paper first introduces the milling technology in Section 2, before presenting the measurement routine in Section 3. Section 4 follows with the simulation setup and procedure for the mill, the results of which form the contents of Section 5. To conclude, the whole work is summarized in Section 6.

2. Milling technology

Traditionally, coal crushers were used for fine to very fine grinding. In these devices, a grinding chamber of cylindrical or conical-cylindrical form turns around its horizontal axis, pulling coal nuts along the machine wall. Because the rotational speed has to remain lower than the centrifugation speed of coal nuts, the installed power is usually relatively low and the necessary time of operation to produce very fine particles is long.

Crushers of greater efficiency, characterized by a still grinding chamber filled with grinding balls put into movement by an agitator, appeared in the thirties. They are known under the term of stirred ball mills. Figure 1 presents a plan of this type of device. Since then, the importance of stirred ball crushers does not stop increasing in the industry and numerous research works arouse from this fact. They are being more and more used for fine and ultrafine grinding in various industrial applications, especially when a high precision and quality of the product is required.

Ball mills are essentially used for the grinding of products in suspensions (wet ball milling). These crushers consist of a grinding chamber partially filled (75-80 % of the volume of the free room) with grinding balls of sizes ranging from 50 to 4000 micrometers made out of steel, glass, ceramic or other – according to the nature and size of the material to be ground. The suspension is fed into the chamber where it mixes with the balls, and is then put into movement by means of an agitator, which typically comes in the form of a rotor with geometrical features. The reduction of size takes place when particles contained in the suspension are captured and compressed during the shocks between balls. Stirred ball mills work either continuously, with a single passage of the suspension in the chamber, or in discontinuous mode. To extract the ground material from the mill, a separation system (sieve) allows its evacuation while maintaining balls inside the chamber [1]. A last operation mode is the so-called batch mode, where a batch of particles and suspension are put into the mill for a predetermined amount of time. No sieve is needed in this case since the batch is extracted at the end of the grinding period; the size of the particles is therefore less controllable.

In the case of very small machines and ground material sizes, one usually talks about stirred bead milling. In these mills, the agitator typically comes in the form of a rotor with geometrical features.

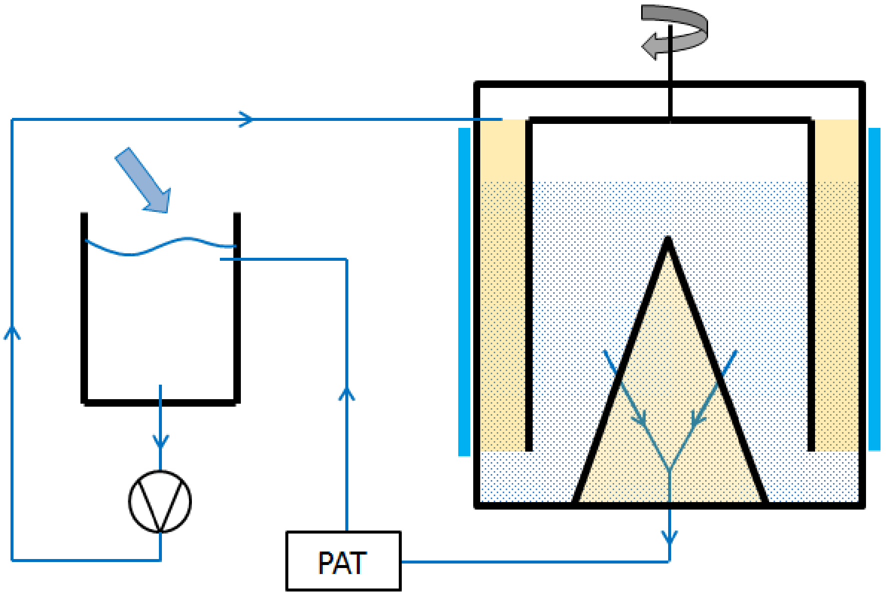


Figure 1. Stirred balls mill schematic, with rotating agitator [1]

3. Experimental measurements

This chapter presents the realization of a test bench at the ENERGY Institute of the University of Applied Science of Western Switzerland in Fribourg, which had for objective to conduct measurements on a NanoWitt-Lab wet bead mill using particle image velocimetry (PIV) in order to study the behavior of the fluid inside the mill and to validate the computational fluid dynamics (CFD) model experimentally. In order to achieve this, multiple sessions of PIV were realized to determine the optimal parameters. Once these were obtained, it was possible to compare the experimental measurements with the simulation results. To be in perfect adequacy with the mill used for PIV, a numerical model was specially created to match the experimental measures. Furthermore, as two solvers were used throughout the project, it was decided to compare PIV to CFD with both ANSYS solvers *CFX* and *Fluent.*

The test bench is shown in Figure 2. It was designed to analyze either bottom or side views of the flow inside the stator with a high speed optical camera. As can be seen in Figure 2, the stator has only flat surfaces in order not to diffract the light, coming from to sources on the sides.

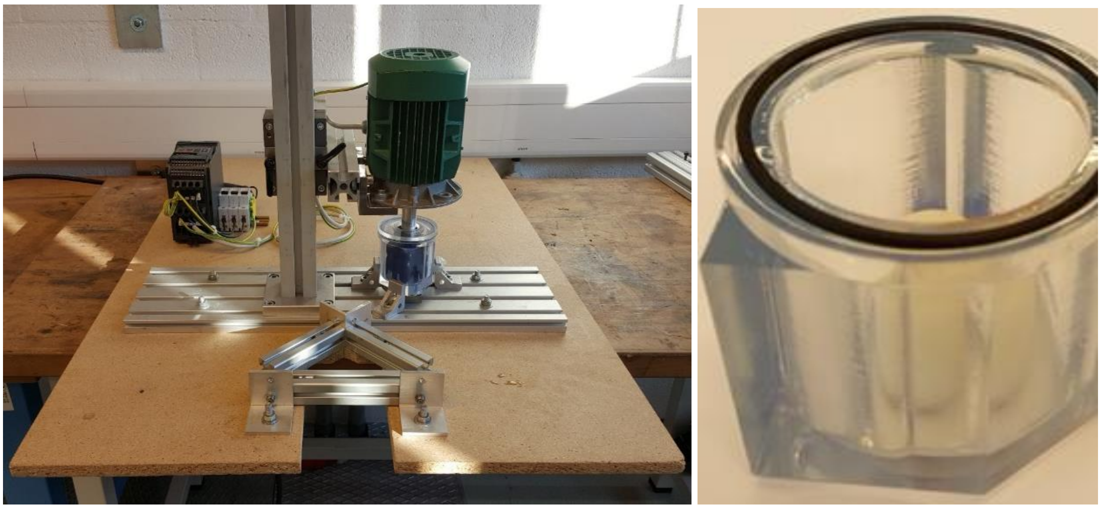


Figure 2. Test bench for PIV analysis (left) and close-up of the stator (right)

3.1 Calibration

The calibration image has for objective to convert pixels in spatial dimension. For that purpose, it is necessary to know the dimensions of a reference object placed in the plane where particles are going to pass. A practical reference is obtained with a grid of black and white squares of known size. Note that one has to be careful not to modify anything in the shooting setup between calibration and measurements. Figure 3 below shows the grid which was immersed in the grinding chamber. Due to the fact that the volume is restricted inside the mill, the size of the grid was reduced as much as necessary, keeping in mind however that the bigger the calibration object, the better the quality of calibration.

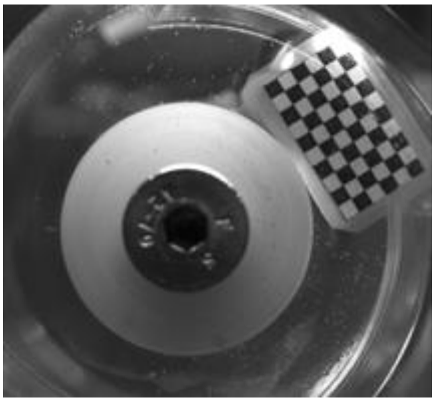


Figure 3. Calibration image with black and white calibration grid

A difficulty in the PIV analysis of this project comes from the fact that the rotor is moving in the background of the particles. Indeed, it is wished to measure the movement of particles on a face situated just in front of the rotor but since it rotates, it is impossible to get the field of speeds close to this particular element. To simulate a fixed rotor face, a Matlab script was created to select the image pairs needed for PIV which contain the rotor in the same position. Thanks to its geometry, one does not have to wait for a full rotation to have an identical position: given that the pump possesses eight blades, an eight of rotation is enough to get the same position again.

3.2 Image treatment

The first stage after having exported the images from the high-speed camera is to cut all image pairs in 90° portions. By using a Matlab program dedicated to this task, it is possible to export a set image pairs spaced out by this angle to handle the fields of speed with rotor blades in a same and unique position. If the black/white contrast on the PIV measurements is of sufficient quality, it is then possible to apply a "wiener" filter to highlight only the white particles on a black background as can be seen in Figure 4.

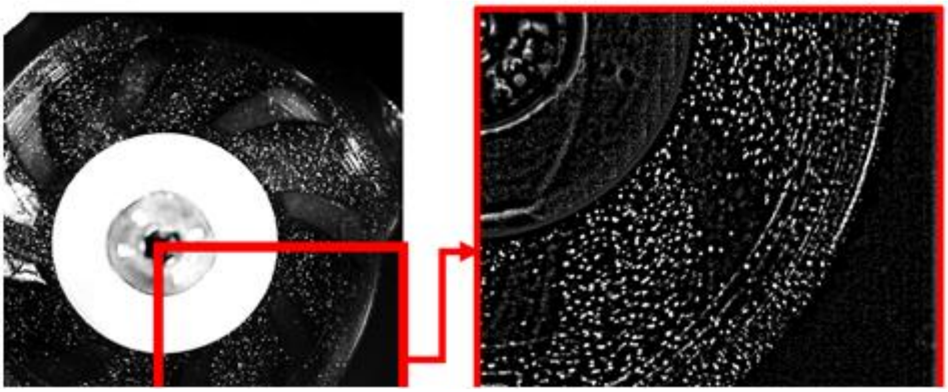


Figure 4. PIV measurement on the original mill without filter (left) and with “wiener” filter (right)

Once the images have been imported and calibrated, a mask is traced on selected areas that are excluded from the PIV measurement zone. All vector fields obtained with the acquisition software are then averaged, and the result is a vector field such as the one shown in Figure 5.

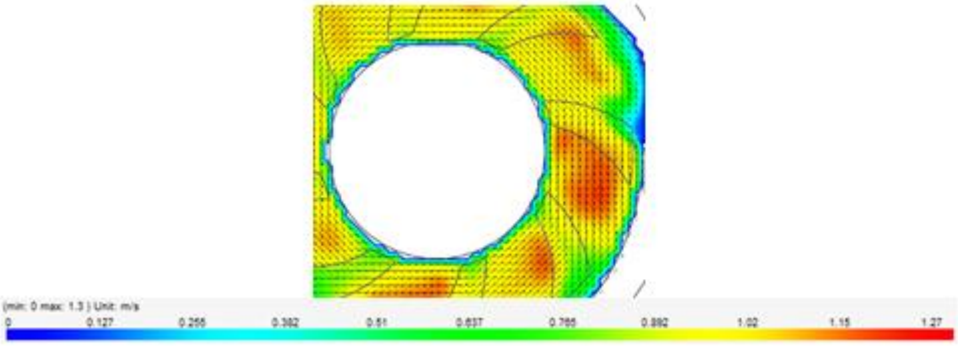


Figure 5. Mean vector field of the particle speeds in the original mill

4. CFD simulations

The main purpose driving the realization of numerical simulations of the grinding mill was not only to obtain a better understanding of the turbulence phenomena inside it and to improve them, but also to obtain a nicer display for a more intuitive flow visualization. This simulation phase was first realized with a simplified model, complemented afterwards with the separator for a complete model of the wet bead mill. The separator was also optimized subsequently.

4.1 Calculation model

At first, the objective was the definition of the optimal calculation conditions for the grinder as well as the choice of CFD simulation tools (turbulence model, meshing and solver). Therefore, a first analysis was conducted on various simplified geometries, staying however as representative as possible of typical cases, in order to obtain results quickly and proceed to experimental tests as expected by the customer. Throughout the project, several more complex geometries were proposed based on the numerical optimization process. Fluid volumes inside the grinding chamber are depicted in Figure 6.

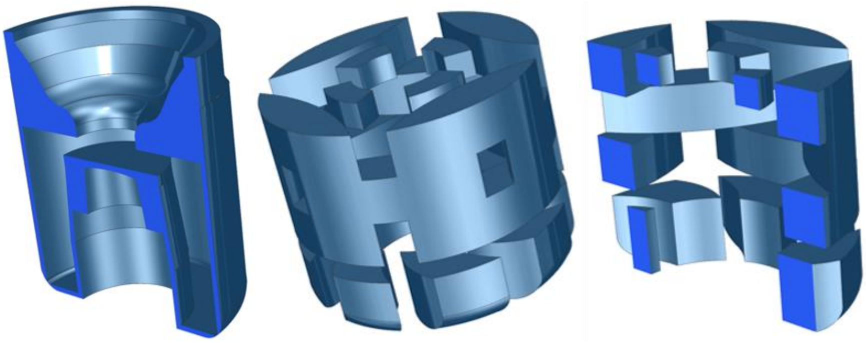


Figure 6. Fluid volume of the stator (left) and rotor (right)

4.2 Mesh

To create a numerical model and impose boundary conditions to it, it is necessary to create the mesh for all mill geometries beforehand. In CFD simulations, meshing represents a crucial aspect because the mesh quality affects directly the quality of the results. Indeed, a bad mesh – too coarse or with too sharp angles in some elements – can lead to incorrect results. For the realization of the mesh, the two possible choices are either to have a tetraedric mesh with prisms near the walls on several layers, or a completely hexaedric mesh. The former being easier to generate, it was used in the early phases to win in time and quickly supply results to the customer. Following these results, the geometry of the rotor could already be improved. At the end of the optimization phase, as the geometry of the rotor and stator were definitive, it was decided to create a hexaedric mesh – generally yielding more accurate results – to confirm the optimized design. For an additional gain of time, only a quarter of the geometry was meshed as can be seen in Figure 7. The apparatus being symmetric, it was possible to duplicate the mesh directly in the solver to re-create a complete mill.

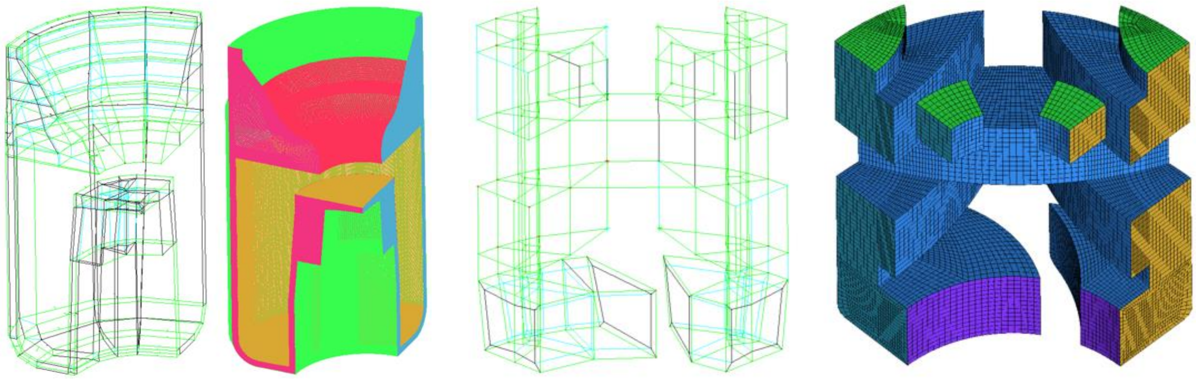


Figure 7. Mesh of the fluid volume of the stator (left) and rotor (right) for CFD calculations

4.3 Boundary conditions and fluid properties

The boundary conditions were chosen so as to represent at best the operating parameters of the mill in closed cycle. A reference pressure value of 101.33 hPa was imposed, corresponding to the atmospheric pressure. Gravity was added to the model with an acceleration of 9.81 m/s2 down. The domain of the rotor was characterized by a rotational speed of 500 rpm. The k-epsilon turbulence model was used in Ansys CFX to solve the fluid equations. As for the fluid properties, this simulation was realized with a Newtonian fluid, the density and viscosity of which were tuned according to the proportion of beads and suspension used. The viscosity was therefore set to a hundred times that of water and the density balanced according to the chosen ratio of suspension to beads in the mix.

The interface rotation of the numerical model is visible in Figure 8. It allows in particular to indicate to the solver that a periodic symmetry is present at the edges of the model, meaning that the highlighted parts are interpreted as if there were distributed several times over 360°. An interface rotor/stator was also introduced between both domains of the model to link the fixed and rotating part.

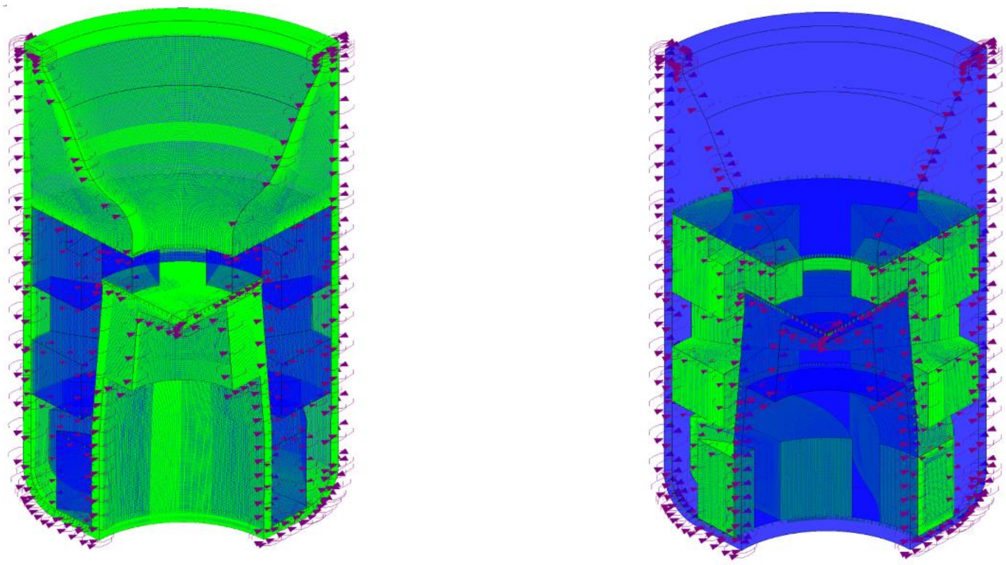


Figure 8. Boundary conditions on the CFD model of the mill

4.4 Simulation results analysis

The numerical simulations were analyzed in the four planes shown in Figure 9. One vertical plane was chosen to have an overview of the axial speed distribution inside the mill in order to determine the flow direction and the degree of turbulence, and three horizontal planes cutting through the rotor were also analyzed since these are zones of interest for radial speed distribution and rotor geometry optimization.

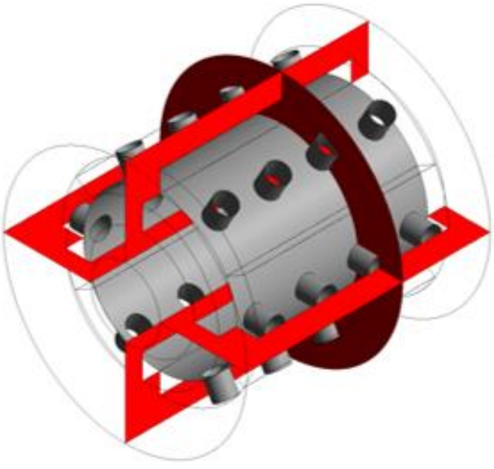
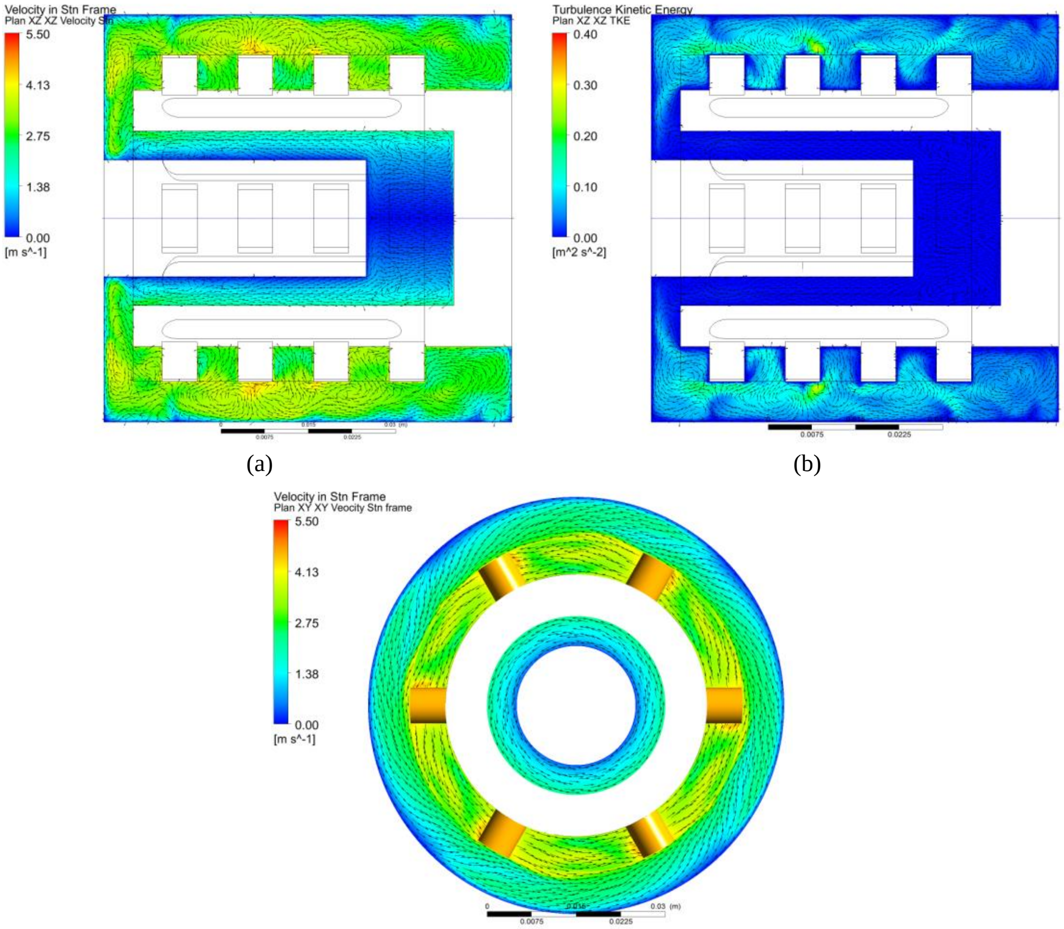


Figure 9. Simulation results planes

The key parameters for the understanding of the flow and the desired operation of the mill are the speed of the fluid throughout the grinding chamber as well as the level of turbulence. The latter indicates the area of the mill where grinding takes place the most effectively, since shocks will occur more often. The results are depicted in Figure 10 in the form of fields of speed and kinetic energy of turbulence on the various. The highest speed of the fluid is 1.57 m/s, as showed in Figure 10 (a) and (b), and it corresponds to the speed of the rotor surface with the largest diameter. Axially, it can be observed well that the flow rises at the outer edges of the mill with a positive speed, and falls towards the center with a negative speed (10 (c)). The study of the kinetic energy of turbulence is more qualitative than quantitative, which is however sufficient to determine if a geometry generates more turbulence than another one and, accordingly, to find an optimal design. One can therefore conclude that this geometry has to be modified and optimized.



(a) (b)

(c)

Figure 10. Fluid velocity and turbulence level inside the mill

5. Results

This section presents briefly the results of both optimization steps, once for the rotor design towards optimal grinding and once for the separator design, aiming for a bead-free active ingredient suspension. It is worthwhile mentioning that the optimization procedure designed in this project is very quick and appropriate for collaborations with the industry thanks to simplifying assumptions in the simulation – however still guaranteeing reliability of the model – and fast prototyping for validation.

5.1 Rotor design optimization

The process described in Section 4.3 was repeated iteratively until a satisfactory geometry for each element could be found, improving the design for more efficient grinding of the active ingredient. The metric for grinding performance is the turbulence level of the flow. The optimization was based both on the number of stages and the stage geometry. Figure 11 shows the results between the original and the final design.

One can see that, beside the geometry optimization, the number of stages was increased from 4 to 7 for a better turbulence level. Note that the maximum number of stages is defined by the manufacturability of the rotor which may vary according to the fabrication process.

With the final design, the cycle length to obtain a given particle size could be reduced, improving also the energy efficiency of the process. This was confirmed experimentally by replacing the original rotor with a ceramic prototype resulting from the optimization process.

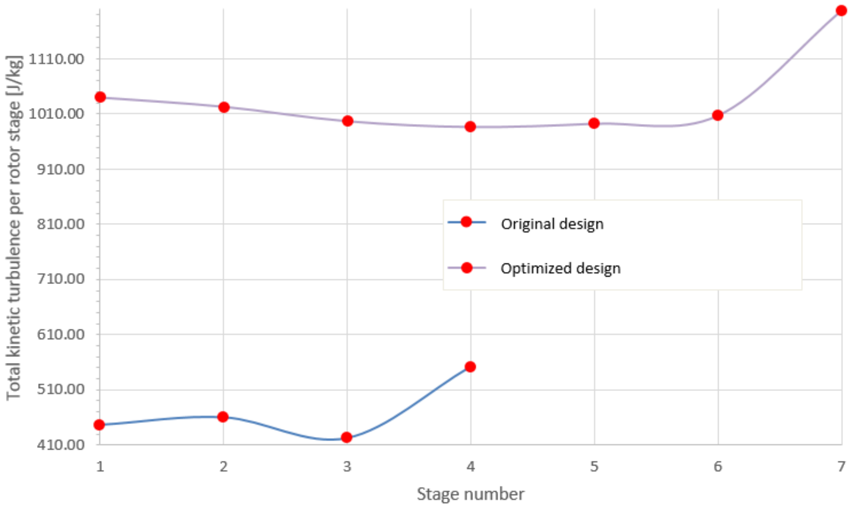


Figure 11. Comparison between the original and optimized design of the rotor

5.2 Separation process optimization

Similarly, a separator was designed and optimized. The obtained final design is exempt of a filter, making it much easier to clean and maintain, and manages to achieve 100% separation between the grinding media – ceramic beads – and the active ingredient suspension. Again, simulations were validated experimentally throughout the whole process since 3D printing technology allowed to fast prototype the different elements of the separator to test each design and make modifications directly when needed.

6. Conclusion

The main achievement of this project is the reduction of the energy need of the wet mill by means of geometry optimization towards more effective grinding. A second completed objective is the integration of a separator without filter to the mill, allowing to extract the active ingredient deprived of grinding beads.

The method implemented to study the behavior of the fluid inside the mill is based on a numerical CFD simulation, validated by PIV measurements realized on a test bench especially designed for this project. The analysis of the simulations allowed to find agitator geometries producing a maximum of turbulence, thus boosting the milling process. Concerning the separation of the grinding media from the active ingredient suspension, a successful solution was found using an iterative process between the design modifications that arouse from the simulations and experimental measurements on the test bench.

The whole optimization and design procedure was conducted in a highly efficient manner, coupling accurate CFD models with empirical data gathered in parallel from the test bench – a feat made possible by fast prototyping of components using 3D printing technology. Thus, a quick and competitive solution could be offered to the industrial partner, with a new optimal wet beat mill that is already being commercialized in the pharmaceutical industry.

7. References

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