Modular spiral jet mill: an innovative tool for targeted micronization of pharmaceutical products

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\textbf{INTRODUCTION}

Approximately 70\% of new chemical entities fall into the BCS Class II category [1], hence requiring application of appropriate pharmaceutical technologies during dosage form development to achieve an improved biopharmaceutical profile. For this class of drugs, the dissolution rate is the key parameter for the in-vitro evaluation of delivery systems. In fact, increasing the dissolution rate could lead to an enhancement in bioavailability and therapeutic effect [2].

Micronization is one of the most popular, robust and reliable processes in the pharmaceutical field for improving the bioavailability of poorly soluble APIs by increasing particle surface area through particle size reduction. The effect of the spiral jet mill on the powder to be milled is related to many geometric and process parameters; in fact, each powder is characterized by a particular physico-mechanical profile and therefore requires a specific mill configuration.

According to literature [3-6] and based on practical experience in using jet-milling equipment, 18 parameters (i.e., 15 geometrical and 3 process parameters) have been identified as critical for their impact on the micronization performance and on the subsequent powder classification capabilities.

This work deals with the development and the testing of a modular spiral jet mill that could be used to generate, theoretically, $2^{15}$ different jet-mill configurations. This modular mill will represent a tool to be used for the micronization and classification performances investigation and optimization.

\textbf{SCOPE}

The aim of this work was to assess that the novel modular jet-mill, assembled to a specific configuration, is able to show the same performance as a standard jet-mill. This goal has been achieved by using as reference the standard MC150 spiral jet-mill (Micromacinazione SA, Switzerland).

\textbf{MATERIALS AND METHODS}

A modular jet mill MM150 (Figure 1) has been set up to simulate the geometrical configuration of a standard MC150 spiral jet-mill.

Lactose Monohydrate (Lactochem\textsuperscript{®}, DFE) was used as model powder for assessing the micronization performance. Design of Experiment (DoE) methodology was used to compare the performance of the two mills within the standard operational range.

In particular, feeding rate (FR) and grinding pressure (GP) were the 2 studied factors. The feeding pressure (FP) was kept always at 1.5 bars higher than grinding pressure.

\begin{itemize}
  \item \textbf{Feeding rate:} 3.22 - 7.74 kg/h;
  \item \textbf{Grinding pressure:} 3.88 - 7.63 bar.
\end{itemize}

The particle size distribution (PSD) results (i.e. Dv10, Dv50, Dv90 and Span) of the lactose milled by both jet-mills (MC150 and MM150) in all the conditions described in Table 1 has been analyzed. The results were considered comparable if they did not differ more than the following values: $\Delta D_{10} = 15\%$, $\Delta D_{50} = 10\%$ and $\Delta D_{90} = 15\%$ (Eu.Ph. Acceptance criteria).

Furthermore, the comparison was also evaluated by considering the overlapping, in terms of area, between the PSD profiles obtained by the MC150 (Reference) and the MM150 (Test).
In particular, the area under the total curve and the intersection area between test and reference curves (see Figure 2) were calculated according to trapezoidal rule for non-uniform grid:

$$\int_{a}^{b} f(x) \, dx \approx \frac{1}{2} \sum_{k=1}^{N} (x_{k+1} - x_{k}) (f(x_{k+1}) + f(x_{k})) \quad (1)$$

The area overlapping was calculated as the ratio between the intersection area and the total curve area multiplied by 100:

$$Area\ Overlapping\ (%) = \frac{Intersection\ Area}{Total\ Area} \times 100 \quad (2)$$

RESULTS

The main results of the DoE study are summarized in Table 1. In particular, the percentage difference between the PSD results achieved with MC150 and MM150 spiral jet-mills were detailed for D10, D50 and D90 percentiles. Moreover, the overlapping results, calculated for each trial, are also reported.

<table>
<thead>
<tr>
<th>Space Type</th>
<th>Grinding Pressure [bar]</th>
<th>Feeding Rate [kg/h]</th>
<th>Dv10 Change (%)</th>
<th>Dv50 Change (%)</th>
<th>Dv90 Change (%)</th>
<th>Span Change (%)</th>
<th>Overlapping (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial 1</td>
<td>7.65</td>
<td>7.74</td>
<td>3.28</td>
<td>11.26</td>
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<td>87</td>
</tr>
<tr>
<td>Axial 2</td>
<td>3.88</td>
<td>3.22</td>
<td>-0.98</td>
<td>-3.74</td>
<td>-15.27</td>
<td>-11.86</td>
<td>91</td>
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<tr>
<td>Axial 3</td>
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<td>5.75</td>
<td>1.45</td>
<td>9.95</td>
<td>7.57</td>
<td>-2.18</td>
<td>87</td>
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<tr>
<td>Axial 4</td>
<td>5.75</td>
<td>5.75</td>
<td>-2.55</td>
<td>1.14</td>
<td>-7.75</td>
<td>-9.30</td>
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<td>5.75</td>
<td>-0.01</td>
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<td>2.60</td>
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<td>-5.06</td>
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</tr>
</tbody>
</table>

Table 1. DoE parameters & results

Results show a percentage difference, for each percentile, always compliant with the acceptance criteria reported in materials and methods. Moreover, in all the cases an overlapping of more than 80% was achieved.

Considering the above, all criteria used for the comparison of the two jet-mills could be considered fully achieved.

CONCLUSION

During this developmental work, it was proved that the modular jet mill (MM150) exhibits the same milling performance as the standard one (MC150).

Based on this positive assessment, the modular jet mill could represent a new tool for process development and optimization being possible to easily change the majority of the geometrical parameters influencing the jet milling performances. This will allow tailoring the required jet mill geometrical configuration on the different pharmaceutical products characteristics.

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REFERENCES


