Multivariate statistical modelling of the pharmaceutical process of wet granulation and tableting
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Granulation of the model drugs, selected in Chapter 2, is examined. Due to the large differences in physical properties between the selected drugs, the design levels of the process variables of the granulation process have to be varied also. The amount of water added during granulation has to be adjusted for each drug to produce granulations that can be further processed into tablets. Chapter 3 describes the determination of an uncritical amount of granulation liquid that can be added to a specific formulation containing lactose, corn starch, polyvinylpyrrolidone and a model drug. Wet granulation proceeds by agitation of a powder mixture in the presence of a liquid. Granules are formed and grow because of effects of mobile liquid bonds formed between the primary particles. Wet granulation in high-shear mixers proceeds within a narrow range of liquid amount. When too much liquid is added, the powder mixture becomes overwetted and cannot be used for tableting. When too little liquid is added, a large percentage of primary particles is still present in the mixture and the granules disintegrate during drying. The uncritical liquid amount could safely be added to the mixture without causing overwetting and the percentage of primary particles decreased to a small amount. The uncritical liquid amount is determined from the power consumption curve of the impeller, obtained during continuous addition of granulating liquid. It is defined as the middle of stage three, according to Leuenberger’s division of the power consumption curve. In the present chapter the uncritical liquid amount is related to physical properties of the model drug. For drugs with a low solubility in the liquid and for drugs that have a large surface area, extra granulation liquid is necessary to produce granules that can be further processed into tablets.

Introduction

In pharmaceutical practice it is well known that wet granulation in high-shear mixers proceeds within a narrow range of liquid contents. The liquid saturation $S$ is claimed to be the major controlling factor for the granule growth process [1–3]. It expresses the
degree of filling the intra granular voids with the binder liquid. It depends on the moisture content relative to dry material of the agglomerates (H), the particle density (ρ) and the porosity (ε). When the powder dissolves partly or totally in the liquid, the relation becomes invalid because the porosity of the particle and the intra granular voids increase.

\[ S = \frac{(1-\varepsilon)}{\text{H}D} \]

According to Kristensen and Schaefer, the liquid amount required to run an uncritical granulation process depends on a large number of factors which include feed material properties, such as the particle size distribution, solubility in the liquid and ability to absorb the liquid [4]. Paris and Stamm also showed the influence of powder quantity, particle size, solubility and the type of granulation liquid on the amount of liquid [5,6]. Prediction of an uncritical amount of granulation liquid on the basis of knowledge of the feed material has not been very successful. Rumpf et al. calculated the cohesive forces that exists between two particles for rhombohedral and for cubical packing assuming ideal wettability and no separation between the particles [7,8]. The cohesive force depends on the surface tension of the granulation liquid, the contact angle, the separation between the particles and the particle diameter. With the cohesive forces, Leuenberger et al. made a theoretical estimate of the quantity of granulation liquid required in the granulation process [9].

For some time now, instrumental techniques have been used to determine an uncritical liquid amount. These techniques include measurement of temperature of the granulation, change in impeller speed during granulation or motor slip [10–13], measurement of power consumption [3,5,6,9,14–20], probes in the powder mass [21] and torque measurement of the main impeller shaft [22,23]. It is found that the measured quantities reflect changes in the rheological properties of the moist mass and that changes are related to the granule growth process. In some papers several techniques for end point control have been compared [24,25]. Corvari et al. found a strong correlation between power consumption and torque measurement.

In a series of articles Leuenberger et al. showed the relation between the power consumption profile of the impeller shaft and the physical properties of the moist mass [9,14-16]. In the power consumption record five different phases can be observed. Figure 4 of Chapter 1 shows a typical power consumption profile given for a lactose/corn starch powder mixture. In the first phase no increase of power consumption is observed because components in the powder mass can take up water and, therefore, no interparticulate liquid bridges are formed. The second phase shows a fast increase of power consumption as liquid bridges are formed. The mass becomes much more cohesive. During phase three the interparticulate void space is filled with granulating liquid. No increase of the power consumption is observed. Within phase three granules can be obtained that differ in their properties. At the start of phase three, porous and
fragile granules will be formed where at the end of the plateau, the granules will be more dense and thus harder. After phase three, parts of the powder mix will be saturated with liquid. This produces lumps in the mixture which causes the power consumption to fluctuate. Finally, the whole mix will be saturated and a suspension will be formed and the power consumption decreases rapidly. The 100% saturation may give a peak in the power consumption profile depending on the type of granulator and material used. In high shear mixers this peak may not be as obvious as in planetary mixers. For the definition of the degree of liquid saturation it is essential to measure the total power consumption profile till the state of a suspension is obtained. Then it is possible to define a normalized value \( S^* \) of the liquid saturation of the interparticulate void space:

\[
S^* = \frac{S - S_3}{S_5 - S_3}
\]

Here \( S \) is the amount of liquid at a certain point in the curve between \( S_3 \) and \( S_5 \), where \( S_3 \) and \( S_5 \) are the boundaries between phase two and three and between phase four and five respectively. \( S^* \) is the percentage the granules are filled up with liquid. Several papers have shown that usable granulations should be obtained at phase three of the typical power consumption profile [5,6,15,17-20,24]. Leuenberger showed the increase of the mean granule diameter, and the decrease of the percentage of fines and granule friability in the range from phase \( S_3 \) to \( S_4 \) [15]. Holm et al. showed that the typical power consumption record only holds for lactose and not for other formulations such as dicalciumphosphate or mixtures of dicalciumphosphate and corn starch [17]. Power consumption profiles vary from product to product. This must be caused by differences of the energy required to rearrange and compact the particles composing the moist agglomerate. The start of the rapid grow of granules, caused by partial saturation of the interparticle voids happens at different liquid saturation levels for different materials. Leuenberger stated that pharmaceutical granules can only be obtained for an amount of granulation liquid in a range up to a degree of saturation of about 60% of the interparticulate void space [15]. Beyond the 60% of liquid saturation the granule size increases exponentially, and lumps will be formed. The same amount is found for a Fielder PMAT 25 VG high-speed mixer [17]. The 60% liquid saturation, however, is only valid for lactose. Holm et al. showed that for other substances, the granule size increases in the same way at other values for the liquid saturation. Dicalciumphosphate has a saturation limit of 70%, dicalciumphosphate/corn starch (85:15) of 85% and dicalciumphosphate/corn starch (55:45) of 90%.

Shiraishi et al. granulated a mixture of theophylline, lactose and corn starch and stopped liquid addition at several points in the power consumption curve [19,20]. Granulation stopped at the start of phase 3 resulted in tablets with the lowest friability and disintegration times. When more water was added, tablet disintegration times increased. Stamm and Paris studied the influence of technological factors and physical
properties of the solvents and products used on the optimal granulation liquid requirement measured by power consumption [5,6]. The optimal liquid amount was calculated according to Leuenberger’s formula: \( S = \frac{1}{2}(S_3 + S_4) \), which corresponded to the liquid amount as determined by particle size investigation. The flow rate showed no influence on the optimal amount. The optimal liquid amount decreases when particle size of the mixture increases. Powders having the same solubility need the same amount of liquid, but granule properties may change due to different wettability properties.

Theoretical evaluations of the maximal liquid saturation are given, but they assume perfect spherical particles [15]. The influence of the various substances on the critical saturation amount can be fairly large. When mixtures of several compounds are granulated, the estimation of the uncritical liquid amount becomes even harder due to large number of factors and the unknown interactions between the various particles. During the granulation, some particles may dissolve partly in the liquid, which leads to very complicated binding forces between the particles. The theoretical model becomes too complicated for common use. Therefore multivariate calibration will be used to model the required liquid amount for several mixtures of lactose and corn starch with varying drugs. The model makes use of the important physical properties of the drugs, under which the particle size distribution, contact angle and solubility in the granulation liquid.

**Multivariate calibration**

Partial least squares regression (PLS) is a biased multivariate calibration technique much used in the field of chemometrics. It can be used instead of ordinary least squares regression (OLS) when serious multicollinearity exists between the descriptor variables or when the number of descriptors exceeds the number of objects. PLS is used to model relations between predictors and response variables and to make predictions. Tutorials on PLS were given by Geladi and Kowalski [26] and by Höskuldsson [27]. PLS finds latent directions in the descriptor data set that have a good relation with the response variable. In Chapter 7, PLS regression will be introduced in detail. Multivariate analysis and calibration in pharmaceutical development work have recently been reviewed by Lindberg and Lundstedt [28].

In the present chapter multivariate calibration is used for the modelling of the uncritical liquid amount (ULA). This amount is defined as \( \text{ULA} = \frac{1}{2}(S_3 + S_4) \), where \( S_3 \) and \( S_4 \) are the start and the end of phase three in the power consumption profile. The profiles were obtained from several powder mixtures consisting of lactose, corn starch and one of the selected model drugs at concentrations of 5% and 50%. The mean granule diameter and the percentage of fines were also measured during stage three of the records. The model can be used to predict uncritical amounts of water that can be added to mixtures of lactose 200 mesh, corn starch, polyvinylpyrrolidone with a new drug.
Experimental

Mixtures of lactose 200 mesh (DMV, Veghel), corn starch (AVEBE) and polyvinylpyrrolidone (PVP 25k, Brocacef) were combined with the model drugs: ascorbic acid, dicalciumphosphate, isoniazid, nicotinamide, paracetamol, salicylic acid, sulfadimidine and thiamine HCl (Pharmachemie). Paracetamol was milled to study the effect of particle size on the uncritical liquid amount. From the eight selected model drugs two different formulations (A and B) were made. Further, a third mixture containing no model drug (C) was granulated. Table 1 shows the percentages of substances in the formulations. Mixture C was considered as mixture A or B with lactose 200 mesh as the model drug.

Power consumption records were obtained from a GRAL 10 high-speed mixer with power consumption measurement supply. Power consumption was measured during continuous liquid addition of water to the mixture. PVP was dry added and water was used as the granulation liquid. Water was added with a peristaltic pump at 30 ml.min⁻¹. During granulation the impeller speed was maintained at 300 rpm and the chopper speed at 1500 rpm. For each experiment 1.5 kg material was used. The records were evaluated and phase three was determined for each mixture. During new experiments, samples were taken from the mixture at several positions in the third phase of the power consumption record. The samples were dried for at least eight hours at 40°C in a tray oven. The samples were screened (2mm) and particle size distribution was obtained by sieve analysis (1.40, 1.12, 0.85, 0.60, 0.425, 0.30, 0.15, 0.00 mm).

Table 2 shows the physical properties of the model drugs that were used for the calibration of the ULA. Sol is the logarithm of the amount of water (g) needed to dissolve 1 g. of drug. The particle size distribution of the drugs was measured by laser diffraction (Sympatic Helos). 10%, 50% and 90% are the boundaries in the particle size distribution curve that indicate that 10%, respectively 50% and 90% of the particles have a smaller particle diameter than the value given. $S_b$ is the surface area $(m^2.cm^{-3})$ based on the bulk of the material. The poured and tapped density $(g.cm^{-3})$ were measured for all drugs. The surface area was also determined by adsorption of $N_2$ (BET). Here also the internal surface area of the pores is included. The contact angle $\theta$ of the drugs was measured by the $h-\epsilon$ method [29]. Lactose 100 mesh is used as a test drug and will not be used in the calibration. The PLS toolbox [30] for MATLAB [31] was used for the calibration calculations of the uncritical liquid amount.

Table 1: Composition of the powder mixtures used in the experiments with 5% drug (A), 50% drug (B) or without drug (C).

<table>
<thead>
<tr>
<th>Component</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>model drug</td>
<td>(%)</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>lactose 200 m</td>
<td>(%)</td>
<td>81</td>
<td>36</td>
</tr>
<tr>
<td>corn starch</td>
<td>(%)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>PVP 15k</td>
<td>(%)</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 2: Physical properties of the model drugs used in the calibration of the uncritical liquid amount and the range. The descriptors are explained in the text.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Sol</th>
<th>10%</th>
<th>50%</th>
<th>90%</th>
<th>S_v</th>
<th>Bulk</th>
<th>Tap</th>
<th>Th.</th>
<th>BET</th>
<th>Cos θ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ascorbic acid</td>
<td>0.54</td>
<td>81</td>
<td>216</td>
<td>398</td>
<td>0.07</td>
<td>0.91</td>
<td>1.00</td>
<td>5.63</td>
<td>0.06</td>
<td>0.78</td>
</tr>
<tr>
<td>dicalciumphosphate</td>
<td>3.70</td>
<td>88</td>
<td>242</td>
<td>375</td>
<td>0.14</td>
<td>0.87</td>
<td>1.00</td>
<td>4.12</td>
<td>0.32</td>
<td>1.00</td>
</tr>
<tr>
<td>isoniazid</td>
<td>0.90</td>
<td>10</td>
<td>39.5</td>
<td>89.0</td>
<td>0.41</td>
<td>0.58</td>
<td>0.78</td>
<td>5.78</td>
<td>0.19</td>
<td>0.66</td>
</tr>
<tr>
<td>nicotinamide</td>
<td>0.00</td>
<td>8.0</td>
<td>25.9</td>
<td>62.3</td>
<td>0.53</td>
<td>0.46</td>
<td>0.68</td>
<td>6.02</td>
<td>0.18</td>
<td>0.70</td>
</tr>
<tr>
<td>paracetamol</td>
<td>1.85</td>
<td>37</td>
<td>360</td>
<td>570</td>
<td>0.11</td>
<td>0.69</td>
<td>0.77</td>
<td>6.56</td>
<td>0.03</td>
<td>0.50</td>
</tr>
<tr>
<td>salicylic acid</td>
<td>2.70</td>
<td>3.0</td>
<td>12</td>
<td>24</td>
<td>1.08</td>
<td>0.28</td>
<td>0.43</td>
<td>5.63</td>
<td>0.41</td>
<td>-0.22</td>
</tr>
<tr>
<td>sulfadimidine</td>
<td>3.70</td>
<td>9.9</td>
<td>54.5</td>
<td>140</td>
<td>0.33</td>
<td>0.58</td>
<td>0.78</td>
<td>5.77</td>
<td>0.07</td>
<td>0.67</td>
</tr>
<tr>
<td>thiamine.HCl</td>
<td>0.00</td>
<td>4.3</td>
<td>20.7</td>
<td>55.0</td>
<td>0.69</td>
<td>0.26</td>
<td>0.43</td>
<td>5.81</td>
<td>0.39</td>
<td>0.64</td>
</tr>
<tr>
<td>lactose 200 mesh</td>
<td>0.70</td>
<td>2.2</td>
<td>26.6</td>
<td>77.3</td>
<td>0.93</td>
<td>0.55</td>
<td>0.85</td>
<td>5.81</td>
<td>0.50</td>
<td>0.80</td>
</tr>
<tr>
<td>lactose 100 mesh</td>
<td>0.70</td>
<td>25</td>
<td>134</td>
<td>223</td>
<td>0.25</td>
<td>0.75</td>
<td>0.85</td>
<td>5.61</td>
<td>0.18</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Results and discussion

Large deviations were found between the power consumption records when the mixture consisted of 50% model drug. When 5% drug was used, only minor differences were found between the records. Therefore, only the 50% mixtures will be considered. Most power consumption records seemed to follow the record of Leuenberger. However, the power consumption records of salicylic acid and milled paracetamol deviated too much from the typical curve of Leuenberger. Both model drugs had very small particles and could not be wetted easily. For these two model drugs, it was not possible to define the start and end of either phase. Therefore, the records of these two model drugs were not used in the calibration.

In the Appendix of this chapter the power consumption records of the model drugs, the mean granule diameter ($d_{ggw}$, mm) at certain stages of the curve and the percentage of fines at the same stages are shown. Samples were taken from the start of phase three with steps of about 1.5 % water until the particle size was too large to fit through the 2 mm screen. The mean granule size at that latest point was set to 3 mm. The percentage of fines ($<150 \mu m$) of the samples is given for all model drugs. For model drugs with a large particle size, the percentage of fines is also given for a larger particle size dependent on the size of the specific drug (o), (lactose 100 mesh, <300 µm; ascorbic acid, <425 µm; dicalciumphosphate, <425 µm; paracetamol, <600 µm).

In each power consumption profile, the five phases can be determined. Large differences exist between the start and end of each phase for the various model drugs. The rise in power consumption in phase two may be steep, as with isoniazid, or may be rather weak as with lactose 200 mesh. The precise start and end of phase three is not always easy to detect from the curves. Phase three starts at the end of the first increase of the power consumption. At the end of phase three the power consumption drops and rises again with more noise than in phase three. For model drugs with small particle
size, a peak arises before the drop in power consumption. For model drugs with a larger particle size, the peak disappears, however, lactose 100 mesh also shows a small peak at the end of phase three. The same peak at the end of phase three was already mentioned by Shiraishi et al. [19]. The end of phase three corresponds well with the exponential growth of the mean granule diameter. In most cases of the drugs with small particle size, the peak at the end of phase three gives overwetting of the mixture. However, for sulfadimidine and lactose 200 mesh this position still gives usable granulations.

For the dicalciumphosphate mixture, only the small particles agglomerate at the beginning of phase three. Dicalciumphosphate does not participate in the agglomeration until the second half of the third phase. Then the amount of particles smaller than 425 µm starts to decrease below 20%. Dicalciumphosphate has a large range of phase three, but good granules can only be obtained at the second half of phase three. The plots of nicotinamide, thiamine.HCl and also ascorbic acid show that before phase three is reached, there is still a large percentage of fines in the mixture. In all of these latter cases the first sample was taken in phase two.

The uncritical liquid amount (ULA = ½(S₂+S₃)) is defined, which is the amount of water that can be safely added to a mixture with lactose 200 mesh, corn starch, PVP and a drug without causing overwetting of the mixture and providing only a small percentage of fines. The figures in the appendix of this chapter show that for all model drugs, the percentages of fines at the ULA is small. For drugs with large particle sizes, the drug particles also take part in the granulation at the ULA. Table 3 shows the mean of two ULA values all model drugs.

Paracetamol was milled to study the effect of particle size reduction. However, the milled paracetamol could not be used in the calibration because of the power consumption record deviation caused by cohesiveness of the material. Therefore, lactose 100 mesh was used to study the effect of particle size reduction on the granulation. For lactose 100 mesh, phase three was reached with less water. The total amount of water to reach phase four is only a little less than for lactose 200 mesh.

<table>
<thead>
<tr>
<th>model drug</th>
<th>ULA for mixtures with 50% model drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>ascorbic acid</td>
<td>8.4</td>
</tr>
<tr>
<td>dicalciumphosphate</td>
<td>13.6</td>
</tr>
<tr>
<td>isoniazid</td>
<td>12.6</td>
</tr>
<tr>
<td>nicotinamid</td>
<td>9.6</td>
</tr>
<tr>
<td>paracetamol</td>
<td>9.2</td>
</tr>
<tr>
<td>salicylic acid</td>
<td>*</td>
</tr>
<tr>
<td>sulfadimidine</td>
<td>14.1</td>
</tr>
<tr>
<td>thiamine.HCl</td>
<td>11.9</td>
</tr>
<tr>
<td>lactose 200 mesh</td>
<td>15.3</td>
</tr>
<tr>
<td>lactose 100 mesh</td>
<td>12.1 / 11.5</td>
</tr>
</tbody>
</table>
Table 4: Results of the calibration of the uncritical liquid amount of granulation liquid

<table>
<thead>
<tr>
<th>% Explained</th>
<th>% X</th>
<th>% y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>87</td>
<td>94</td>
</tr>
</tbody>
</table>

PLS regression was used for the calibration of the amount of water to reach the ULA. The descriptor variables were autoscaled so they all would have the same weight. The ULA values were mean centred. Table 4 shows the results of the calibration.

For the PLS model of the uncritical liquid amount, three PLS factors were selected with cross validation, which explained 94% of the variance in the response variable. The root mean squared error (RMSE) of the model is comparable to the experimental error (s). RMPRESS is somewhat higher. $Q^2$ gives the squared correlation between the leave one out predictions and the measured ULA values. The separate training sets in the cross validation steps were not mean centred. This would increase the extrapolation of the models because only eight, rather different, drugs were used in the modelling. Three PLS factors are rather high for the model, however, PRESS kept decreasing when more factors were included. Figure 1 shows the predicted vs. observed ULA. Lactose 100 mesh was also used as a test drug for the calibration. The measured ULA values were compared with the predicted values by the PLS model. The predicted ULA values of lactose 100 mesh are also given (※). The predicted value corresponds rather well with the measured ULA values.

Table 4 also shows the regression coefficients that were calculated from the PLS factors. The ULA can be predicted according to the next formula:

$$ULA = 11.8 + 1.8 \text{ (Sol) } - 0.8 \text{ (10%)} - 0.3 \text{ (50%)} - 0.3 \text{ (90%)} + 0.7 \text{ (S_v)} + 0.5 \text{ (Tap)} - 0.3 \text{ (Thick)} + 0.8 \text{ (BET)}$$

A strong relation exists between the amount of water that can be added to the mixture and the surface of the specific drug during granulation. The surface area comprises the outer and inner surface of the particles. Drugs with large surface area (high $S_v$ and BET) have high ULA values. The negative sign of the regression coefficient of (10%) indicates that drugs without small particles need less water than drugs with small particles. Drugs that dissolve easily in the liquid (low sol) only need a small amount of water to reach the ULA. During water addition, part of the model drugs may dissolve in the water. This leads to a decrease of the surface area.

The total range of phase three (Range=$S_4-S_3$) could not be described by the physical properties of the model drugs. No explanation could be found why some drugs start to
agglomerate earlier than others. The comparison between lactose 100 mesh and lactose 200 mesh shows that the first starts to agglomerate with less water than lactose 200 mesh.

The ULA for mixtures with lactose 200 mesh, corn starch, PVP and a drug can be predicted rather well with the model. One must keep in mind that only 8 model drugs are used in the calibration, however these drugs were selected to have a broad range in physical properties. For a better prediction model, more drugs are to be used, or the drugs have to be more similar. A limitation however is that for drugs with very small particle size (such as salicylic acid and milled paracetamol) the model cannot be used. The power consumption records for such drugs were too different from the regular curve given by Leuenberger, that was found for the rest of the model drugs.

**Conclusion**

Mixtures of lactose 200 mesh, corn starch, PVP with several model drugs at the 50% level have been studied. Power consumption curves have been recorded for several drugs that were selected to have large spread in physical properties. In was shown that during phase three of the records, the mean granule size increases and the percentages of fines decreases. An uncritical liquid amount (ULA) was defined to be in the middle of phase three. The ULA is the safe amount of water that can be added to the powder mixture without causing overwetting of the mass. The percentage of fines
at the ULA was very small for all model drugs. The ULA was related to physical properties of the drugs that were used. The surface area of the particles and the solubility of the drugs are of main importance for the amount of water that can be added. Drugs with a large surface area can take much water before overwetting will occur. Drugs with high solubility in the liquid, tend to dissolve during granulation. Therefore, the surface area of the powder mixture decreases and only a small amount of water can be added. The calibration model can be used for prediction of liquid amount that can safely be added to mixtures of lactose 200 mesh, corn starch, PVP and a new drug.

References


30. PLS Toolbox for Matlab, Eigenvector Research Inc., Manson WA, USA.

31. Matlab is a registered environment for matrix calculations, The Mathworks Inc., Natick, MA, USA.
Appendix

Figure A and B: Mean particle size, power consumption profile and percentage of fines (*=<150µm, o=<425µm) for ascorbic acid and dicalciumphosphate.
Prediction of the uncritical liquid amount in wet granulation

Figure C and D: Mean particle size, power consumption profile and percentage of fines (*≤150µm) for isoniazid and nicotinamide.
Figure E and F: Mean particle size, power consumption profile and percentage of fines (*=<150µm, o=<600µm) for paracetamol and sulfadimidine.
Figure G and H: Mean particle size, power consumption profile and percentage of fines (*=<150µm) for thiamine.HCl and lactose 200 mesh.
Figure I: Mean particle size, power consumption profile and percentage of fines (✦=<150µm, ○=<300µm) for lactose 100 mesh.