Chapter 8
The granule growth regime map, is it suitable to predict granule growth behaviour?

8.1 Summary
Granule growth behaviour can be explained using the growth regime map. However, some of our previous results raised doubts on the predictive value of this growth regime map, since the experimental results could not be filled in the map using the described equations [1]. Therefore, the vertical drop experiments used to describe the deformability of wet material as performed by Iveson et al. [2, 3] were repeated.

Most powder-liquid combinations were found where expected in the map. However, the experimental errors (inherent to the method) result in extremely large variations, overlapping all growth regimes. This shows that Stokes deformation number cannot be measured unambiguously. Until it has been improved, the growth regime map can be used as guidance only, not for prediction of the different growth regimes happening during granulation.
8.2 Introduction

In an attempt to clarify all effects occurring in a granulation procedure, Iveson and Litster introduced the growth regime map [3, 4]. In this map maximum pore saturation of granules is plotted against wet granule deformability (Figure 1). It shows that if not enough liquid is present; granules do not grow (nucleation only). At a little higher liquid content, induction type behaviour occurs when granules are so strong that they do not deform sufficiently to coalesce. Growth occurs by layering of fines [5]. When the granules are more deformable, they grow linearly with time, which shows steady growth regime. The more deformable the granules, the weaker they become, finally ending in the crumb regime, where granules break upon impact with impeller, chopper, or wall. Finally, if too much liquid is present, the material becomes overwetted, ending as slurry.

\[ S_{\text{Stokes deformation number}} = \frac{\rho_g \cdot v_c^2}{2\sigma} \]

\[ s_{\text{max}} = \frac{v \cdot \rho_f \cdot (1 - \varepsilon_{\text{min}})}{\rho_f \cdot \varepsilon_{\text{min}}} \]

**Figure 1:** Growth regime map according to Iveson et al. [94]

The growth regime map, as an explanation of the granulation growth behaviour, is a useful tool to structure thoughts about the granulation process [1, 6]. For instance, an increase in binder viscosity leads to lower granule deformability and a different granulation regime can be obtained. Another example is an increase in liquid amount leading to increased pore saturation and an increase in deformability.
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These examples can be extracted from the regime map, and have been proven to be correct [1]. However, some of our previous results raised doubts on the predictive value of the growth regime map, since the experimental results could not be filled in the map using the described equations [1]. Not only has the mathematical way of determining deformability raised questions, also the method of measurement of deformability. Iveson and Litster use at least 50 measurements to obtain one data point in the chart, indicating large variations [2]. This could be expected: when looking at the method of measurement chosen it is clear that a small mistake in measurement of the cylinders diameter leads to a large variation. Moreover, the way the cylinders were prepared also induces large variations in their porosity, and the reproducibility of this method is questionable. Another problem is encountered in both the mathematical and the practical method: the parameters necessary to calculate deformability are multi-interpretable. This leads to large errors, since the smallest deviation already has a too large effect on the value of deformability. Finally, the boundaries between the different growth regimes cannot clearly be set. Iveson and Litster used a couple of materials to indicate the boundaries [2]. However, the materials they used to check their regime map were all completely plastically deforming materials. It would be worthwhile to know whether the growth regime map or a derivative of it could also be used for other materials, therefore we investigated whether other materials can also be placed in this map using the experiments as performed by Iveson et al. [2, 3].

8.3 Materials and methods

The vertical drop experiments as performed by Iveson et al. [2, 3] were performed on different materials. Liquid and powder were hand-mixed and kneaded in a plastic bag. Microcrystalline cellulose (Pharmacel® 101, DMV International, Veghel, the Netherlands), α-lactose 450M (Pharmatose® 450M, DMV International, Veghel, the Netherlands), and dextrin (Primogran W (lot 45P/EP), Avebe, Foxhol, the Netherlands) were used with different liquid contents. Lactose was also mixed with an aqueous HPC solution (17% HPC solution, with a viscosity of 3 Pa·s) (Hydroxypropylcellulose, lot 59H0637, Sigma-Aldrich Chemie GmbH, Steinheim, Germany).

After mixing, the wet material was compacted in a 13 mm diameter die with 50 N using a hydraulic press (ESH compaction apparatus, Hydro Mooi, Appingedam, The Netherlands). Compaction rate was 5 N/s and the maximum pressure was maintained for 0.1 s.

The wet compacts were dropped from 0.9 m flat face first onto a stainless steel plate. Unfortunately, the compacts were often not parallel to the plate at impact, leading to a partly oblique cylinder (see Figure 2).
Figure 2: A schematic representation of the cylinders after the vertical drop experiments (A) from Iveson et al. [2] and (B) our own results. Note that the deformed area is drawn on the top.

Dynamic yield stress \( Y \) was calculated according to Equation 1, in which \( \rho_g \) means density of the wet compact, \( U_c \) means the velocity of the wet cylinder during impact, \( A_0 \) means the 2D area before impact, and \( A_1 \) the area after impact. We measured the unchanged surface area and the newly formed area, and added these values to obtain the \( A_1 \) value.

\[
Y = \frac{\frac{1}{2} \cdot \rho_g \cdot U_c^2}{\frac{4}{3} - 1 + \ln\left(\frac{A_1}{A_0}\right)}
\]

Equation 1 [2]

This dynamic yield stress was used in the equation for Stokes deformation number according to equation 2.

\[
St_{def} = \frac{\rho_g \cdot U_c^2}{2Ya}
\]

Equation 2 [3]

Pore saturation \( s_{\text{max}} \) was calculated according to equation 3, and it was corrected for the solubility in the liquid binder according to Hoornaert et al. [7]. In this equation \( w \) means the mass ratio liquid to solid, \( \rho_s \) is the density of the solid particles, \( \rho_l \) is liquid density and \( \varepsilon_{\text{min}} \) is the minimum porosity reached by that powder-liquid combination in the particular operating conditions.

\[
s_{\text{max}} = \frac{w \cdot \rho_s \cdot \left(1 - \varepsilon_{\text{min}}\right)}{\rho_l \cdot \varepsilon_{\text{min}}}
\]

Equation 3 [7]
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8.4 Results and discussion

8.4.1 Experiences performing the vertical drop experiments
Many disadvantages were encountered in using the vertical drop experiments. First of all, the cylinders used are larger than granules, thus needing a higher internal strength. Secondly, there will be a porosity difference. In granules a porosity difference can be found in the radial direction [8], however, in the cylinders a porosity difference in the vertical direction will be found. Therefore, the side on which the cylinders fall is of importance, since a higher porosity will lead to an increased deformation. Finally, to obtain a low porosity, sometimes excess liquid will be squeezed out of the mould, whereas during granulation this excess liquid will be used for growth.

8.4.2 Deformability of the visco-elastic materials
Some of the powder-liquid combinations resulted in frequent breakage of the cylinders, as shown in Table 1. These cylinders completely shattered upon impact. The wet porosity of these cylinders was higher than of those that stayed intact, although for lactose the difference between the wet porosity of broken and non-broken cylinders is small. However, it shows that densification to a certain extent is necessary to keep the compact intact, dependent upon the powder-liquid mixture.

Table 1: Experiences using vertical drop experiments

<table>
<thead>
<tr>
<th>Material</th>
<th>Amount of cylinders</th>
<th>Wet porosity (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose liquid</td>
<td>14 broken</td>
<td>$\varepsilon = 0.18$</td>
</tr>
<tr>
<td></td>
<td>30 non-broken</td>
<td>$\varepsilon = 0.17$</td>
</tr>
<tr>
<td>Lactose liquid</td>
<td>12 broken</td>
<td>$\varepsilon = 0.16$</td>
</tr>
<tr>
<td></td>
<td>29 non-broken</td>
<td>$\varepsilon = 0.12$</td>
</tr>
<tr>
<td>MCC liquid</td>
<td>5 broken</td>
<td>$\varepsilon = 0.35$</td>
</tr>
<tr>
<td></td>
<td>29 non-broken</td>
<td>$\varepsilon = 0.22$</td>
</tr>
<tr>
<td>Dextrin liquid</td>
<td>9 broken</td>
<td>$\varepsilon = 0.28$</td>
</tr>
<tr>
<td></td>
<td>30 non-broken</td>
<td>$\varepsilon = 0.21$</td>
</tr>
<tr>
<td>Dextrin liquid</td>
<td>3 broken</td>
<td>$\varepsilon = 0.19$</td>
</tr>
<tr>
<td></td>
<td>30 non-broken</td>
<td>$\varepsilon = 0.15$</td>
</tr>
</tbody>
</table>

Although it was tried in all experiments, no cylinder fell flat-face first. It was impossible to arrange the drop in a way that only the top surface was undergoing impact. Pictures of Iveson and Litster [2] show a similar pattern, since their deformed surface also resulted in an elliptical shape. Next to that, all our cylinders bounced (except for the broken cylinders, they shattered during impact), showing
elastic behaviour. When looking at the two-dimensional deformation only, we measured the deformed surface area (shown in Table 2). Surprisingly, the amount of deformed surface area was not always higher at a higher liquid content (lactose, dextrin). However, in these cases the wet porosity was also low compared to the other cylinders, resulting in a stronger wet compact, thus leading to a lower deformed area. When using a viscous binder solution (lactose-HPC), the cylinder became even stronger and the amount of deformed area decreased even more.

When Stokes deformation numbers were calculated using the results of the vertical drop experiments, Figure 3 was found. The highest value of Stokes deformation number was found for lactose 18% w/w water. In the high shear granulation process, this powder-liquid combination shows crumb behaviour. Upon increasing liquid amount (lactose 21% w/w water), a slurry is obtained. Maximum pore saturation greatly exceeds 1 in this case. When a HPC solution is used as a binder in high shear granulating α-lactose, it shows steady growth behaviour [111]. However, it has to be kept in mind that the experimental errors (inherent to the method) result in extremely large variations. The variation was calculated by assuming a variation in measuring the deformed area. This leads to an average variation of 0.015 (200-1700%) in the value for Stokes deformation number. It is redundant to say that this error overlaps all growth regimes. Despite the large error in measurement, most powder-liquid combinations were found where expected.

<table>
<thead>
<tr>
<th>Material</th>
<th>Liquid amount</th>
<th>Wet porosity (-)</th>
<th>Dry porosity (-)</th>
<th>% deformed surface area</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Lactose</td>
<td>18%</td>
<td>0.17</td>
<td>0.29</td>
<td>27</td>
</tr>
<tr>
<td>α-Lactose</td>
<td>21%</td>
<td>0.12</td>
<td>0.32</td>
<td>20</td>
</tr>
<tr>
<td>α-Lactose-HPC</td>
<td>18%</td>
<td>0.16</td>
<td>0.31</td>
<td>15</td>
</tr>
<tr>
<td>MCC</td>
<td>75%</td>
<td>0.22</td>
<td>0.62</td>
<td>9</td>
</tr>
<tr>
<td>MCC</td>
<td>100%</td>
<td>0.14</td>
<td>0.61</td>
<td>10</td>
</tr>
<tr>
<td>MCC</td>
<td>125%</td>
<td>0.07</td>
<td>0.63</td>
<td>18</td>
</tr>
<tr>
<td>Dextrin</td>
<td>38%</td>
<td>0.21</td>
<td>0.51</td>
<td>10</td>
</tr>
<tr>
<td>Dextrin</td>
<td>40%</td>
<td>0.15</td>
<td>0.50</td>
<td>8</td>
</tr>
<tr>
<td>Dextrin</td>
<td>50%</td>
<td>0.14</td>
<td>0.51</td>
<td>11</td>
</tr>
</tbody>
</table>

For microcrystalline cellulose (MCC), an increase in deformation number was found at increasing liquid content, complying with expectations. MCC 75% w/w water shows nucleation only behaviour, whilst higher liquid contents show steady growth behaviour.

When looking at dextrin, the lowest liquid content (38% w/w water) shows the lowest deformation, although the difference with the little higher liquid content (40% w/w water) is small. In granulation, the difference between these two liquid
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contents is high. Dextrin 38% w/w water shows induction type behaviour, whereas dextrin 40% w/w water shows steady growth. Dextrin 50% w/w water shows an even higher deformability, however, in granulation this powder-liquid combination leads to slurry. Relative to the other materials and conditions, these measurements comply with expectations. However, when placed in the map used by Iveson et al. [3], the results do not fit. For example, MCC 75% w/w water is not found in the nucleation regime, and dextrin 38% w/w water is not found in the induction regime. Most of the powder-liquid combinations show steady growth behaviour, although only some of them are found in this region of the map. Lactose 18% w/w water is not found in the crumb region, although in granulation it shows crumb behaviour.

Figure 3: The results of the vertical drop experiments placed in the map of Iveson et al. [94] Legend: □ steady growth behaviour, ▲ slurry, x nucleation only, ◦ induction type behaviour, and * shows crumb behaviour. Clearly the results are not consistent with the original borders between different granule growth regimes. The average variation in the measurement is 0.015 in Stokes deformation number.

These deviations from the expected results can be explained in three ways. First of all, the lines indicating the different growth regimes could not be drawn correctly. Secondly, the way of measuring deformation is a problem. The vertical drop test has a too large variation to be unambiguous, at least for the experiments carried out with the visco-elastic deforming wet materials. Moreover, the amount of measurements carried out by Iveson et al. to obtain one data point give rise to the idea that in their case tests led to large variations. It shows that the method of measuring used is not unambiguous, and therefore not suitable. Finally, the question arises whether the parameters chosen in the growth regime map are
correct. Perhaps wet granule strength would be a better tool to use, it would show crumb behaviour easily. Using wet granule strength would require a good method to measure wet granule strength. However, previous papers showed that this is rather difficult too [8].

8.5 Conclusion

In granulation the growth regime map is a useful tool. A quick method to assess the growth regime is described in our material exchange study [1]. However, values for Stokes deformation number cannot be measured unambiguously. Therefore, a new method for determining deformability should be investigated, or another parameter should be used instead of Stokes deformation number. Until it has been improved, the growth regime map can only be used as a guidance to order different occurrences happening during granulation.

8.6 Symbols

\begin{itemize}
\item $A_0$: 2D area before impact
\item $A_1$: 2D area after impact
\item $s_{\text{max}}$: Maximum pore saturation
\item $St_{\text{def}}$: Stokes deformation number
\item $U_c$: Velocity of wet cylinder during impact
\item $v_c$: Representative collision velocity
\item $w$: Mass ratio liquid to solid
\item $Y$: Dynamic yield stress
\end{itemize}

\textbf{Greek symbols}

\begin{itemize}
\item $\varepsilon_{\text{min}}$: Minimum porosity reached in a particular powder-liquid combination
\item $\rho_l$: Liquid density
\item $\rho_g$: Granular density
\item $\rho_s$: Density of the solid particles
\item $\sigma$: Wet granule strength
\end{itemize}

8.7 Literature

1. Bouwman, A.M., et al., \textit{The use of Stokes deformation number as a predictive tool for material exchange behaviour of granules in the ‘equilibrium phase’ in high shear granulation.} (Chapter 6).
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