Chapter 9
Conclusions and recommendations

9.1 Conclusions

In the granulation process many parameters play a role, and changes in each of the individual parameters can affect several others. This leads to a complex concept of the granulation process, and it shows why the process after decades of research is still not completely understood. In this thesis one of the goals of granulation is investigated: to determine in which way granule shape is influenced by material properties and process conditions. As shown in Chapter 1, many factors influence shape. A simplified scheme of the major variables is shown in Figure 1.

![Figure 1: A schematic representation of the major variables that affect granule shape in high shear wet granulation.](image)

The central position in this figure is granule growth. The way granules grow determines the eventual shape of the granule. For instance, if crumb behaviour
occurs, granules are crushed completely into small pieces upon impact. These pieces are rebuilt into granules. The effect is an irregular surface, and poor sphericity. The steady growth regime is the most optimal growth regime to obtain spherical granules. The granulation mechanism can easily be shown using colour exchange experiments (Chapter 6).

The granulation regime can be changed by variations in a number of variables. Granule deformability is important for the granulation regime. This deformability can be adjusted by changing liquid content (Chapter 7) or liquid viscosity, indirectly also altering granule shape. Unfortunately, granule deformability cannot accurately be measured (Chapter 7&8), nor calculated (Chapter 8), so from the materials only it cannot be predicted.

The nucleation mechanism also affects granule growth mechanism. If a broad nuclei size distribution is obtained, a small granule size distribution has become impossible (Chapter 4). Nucleation determines the granulation process, but among other things, equipment properties affect the nucleation process. For instance, the contact angle of the vessel wall in relation to the sorption rate of the powder used determines the nucleation process. A high contact angle of the vessel wall material, combined with a fast imbibing powder lead to a good distribution of liquid over the powder bed, thus resulting in a small particle size distribution (Chapter 3).

Powder properties, or more accurately the properties of the wet powder mass are also highly influential. Stickiness of the wet material (measured using torque), influenced by liquid content, is also important for growth rate and wet granule strength. Wet granule strength together with wet granule deformability determine whether a granule densifies and grows upon impact, or whether the granule will break, thus ending in the crumb regime.

In summary, depending on powder material (particle size, specific surface area, liquid sorption rate), binder liquid (viscosity, amount), equipment properties (vessel wall material, type of mixer, fill grade), and process conditions (impeller speed, chopper speed, mixing time) a certain nucleation regime followed by a granulation regime is obtained, which leads to a certain granule shape.

### 9.2 Recommendations

Although the above shows the underlying correlations between powder and binder material, process conditions, and finally granule shape, we are still far away from the wish to predict granule shape from materials and process conditions only.

Using Figure 1 again, now starting at the left side; it is clear that we should know the influence of different mixers. Experience tells us that a difference in mixer type can lead to a large deviation in granulation behaviour. It would be worth investigating how to compare these mixer types, and especially how to rescale from one type to another. Possibly some kind of ‘rescale’ dimensionless number can be created, which tells something about the type of mixing.
Conclusions and recommendations

Although it seems that nucleation in high shear granulation is optimal when liquid is poured on the powder bed at once, it might be worth investigating whether this idea is true. Lactose, for instance, is sensitive towards the amount of liquid used as a binder in high shear granulation. However, in the vertical drop experiments we could increase the amount of liquid without any problem. Perhaps it is possible to increase liquid amount in granulation as well (with the advantage of larger granules) when liquid is added slowly or is sprayed onto the bed.

The main question still to be answered is that of wet granule strength/wet granule deformability. A method should be derived that can measure these parameters accurately, not only for completely plastic wet masses, but also for visco-elastic wet materials. This might be done by measuring material exchange kinetics, since this tells something about wet granule strength.

Ultimately, all effects might be used to design a granulation model, in which the starting materials and equipment are the input, and the granule size distribution and granule shape are the output.

9.3 Practical tips

Several suggestions to optimize the granulation process to end up with spherical particles:

- Ensure all powder is participating in the process immediately from the start. Powder must not stick to the vessel wall or lid, or, even worse, in a stagnant zone in the granulator. For example when the chopper speed is too low compared to the impeller speed, powder is accumulated before the chopper.

- Some powders need special care before they can be granulated. Lactose for example must always be dry mixed before the granulation procedure starts. This is necessary to create a bed porous enough for the liquid to immerse sufficiently. If the powder is not aerated, the granule size distribution will be broad.

- Granulation should preferably be performed in the steady growth regime.
  - If in crumb: increase viscosity of the binder fluid
  - If in nucleation only: increase liquid content
  - If in induction type behaviour: increase liquid content or decrease massing time

- If the granule is so deformable that due to the deformability it continuously breaks, viscosity should be increased to increase granule strength.

- In small scale (research purposes) not only a similar mixer type should be used as in large scale, but also a vessel material must be chosen that has similar properties as that used in large scale production.