Continuous twin-screw granulation – Analysis of process parameters and process scale-up

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INTRODUCTION

Twin-screw granulation (TSG) has a significant advantage over traditional granulation methods: the possibility of continuous manufacturing. As can be shown in this study it is possible to tailor particle size distribution of the granules by changing the process parameters or screw configuration. The most important process parameters and their influence on product quality as well as crucial parameters on scale-up are summarized in this study.

MATERIALS AND METHODS

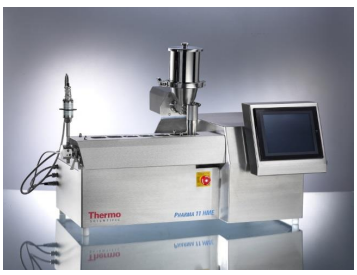
The granulation has been performed on three different scales: The Thermo Scientific® Pharma 11 benchtop extruder (see Figure 2), the Thermo Scientific® Pharma 16 (see Figure 4) and the Thermo Scientific® TSE 24. The screw elements of these different scales are shown in Figure 1. The geometry of the screws and the barrel scales directly, i.e. the same ratio of the inner and outer diameter and the same screw clearance ratio. Therefore, these machines can be easily compared.

Figure 1. The three scales in this study: 11 mm, 16 mm and 24 mm sized twin-screws.

For this analysis a placebo formulation has been used: A dry pre-blend of 62.8% lactose, 32% corn starch, 5% PVP 30 and 0.2% talcum. To feed the solid pre-blend into the barrel, a gravimetric twin-screw feeder has been used for each scale. Water as liquid binder has been fed into the barrel by a peristaltic pump. The granules have been analyzed in-line using the Eyecon$_2$ Particle Analyzer (Innopharma Technology) and at-line with a Retsch® sieve analysis after drying. On all scales a full factorial DoE has been performed changing the process parameters independently. The residence time distribution has been measured on the Pharma 16 using a UV-sensor.

RESULTS

Figure 2. Thermo Scientific™ Pharma 11 benchtop twin-screw extruder.



The influence of TSG process parameters on the mean particle size ($d_{v,50}$) the particle size distribution (PSD) and the granule density ρ_G is summarized in Table 1.

Table 1. Influence of TSG process parameters on granule attributes.

Increase of…	Effect on		
Process parameter	$d_{v,50}$	PSD	ρ_G
…liquid-to-solid ratio	+	0	+
…throughput	+	+	+
…screw speed	-	-	
…intensity of mixing (screw configuration)	+		+
…temperature	+	0	+

An increase in throughput e.g. results in an increase in the filling level of the screws. Thus, stronger kneading and compaction is performed. In general, lower screw speeds and higher throughputs increase the filling level resulting in larger particles (see Figure 3).

Figure 3. Surface plot of the mean particle size ($d_{v,50}$) over throughput and screw speed.

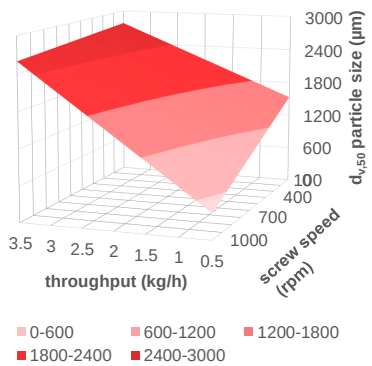


Figure 4. Thermo Scientific™ Pharma 16 production scale twin-screw extruder.

For scale-up of the TSG process the filling level within the screws and the residence time distribution are crucial. Figure 5 shows the mean residence time of the material within the Pharma 16 extruder. For most throughputs the mean residence time decreases with increasing screw speed. But at a very low throughput and high screw speed a sharp increase of mean residence time is obtained. This is due to the low filling level of the screws resulting in a poor conveying behavior. An increase of particle size due to this mechanism has also been reported by Kumar et al..

Considering these effects the TSG process can be scaled-up successfully. Figure 6 shows the accumulated particle size of dry granules obtained on the Pharma 11 and the Pharma 16.

Figure 5. Mean residence time during granulation on the Pharma 16

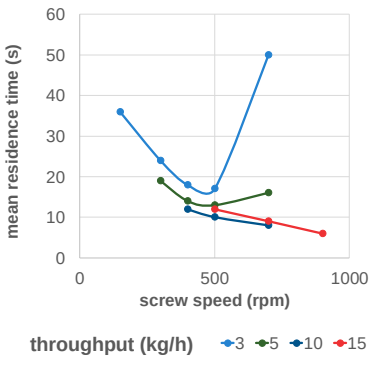
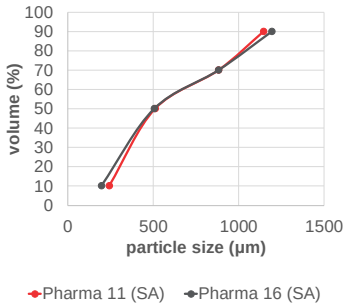


Figure 6. Particle size distribution from sieve analysis (SA) of granules obtained on two different scales



CONCLUSIONS

- The exemplary results show the importance of process understanding of continuous twin-screw granulation.
- All process parameters (total throughput, liquid-to-solid ratio, screw speed and barrel temperature) as well as the screw configuration can change the granule quality significantly.
- Based on this the granule attributes can be tailored.
- Extreme regimes, e.g. a wide residence time distribution, result in a strong change in granule quality. A scale-up in these regimes c problematic (see Osorio et al.).
- The granule quality produced on the small scale is predictive for granule quality obtained on a larger scale.
- All results are also valid for the 24 mm scaled extruder (not shown here).
- This concept has also been proved in continuous wet granulation including the drying process (Glatt® MODCOS xs-, s- and m-line).

REFERENCES

Kumar et al., Eur. J. Pharm. Biopharm. 87 (2014) 279–289.

Osorio et al., AIChE J. (2016).

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