White paper

Continuous twin-screw granulation leads to faster process development and reliable scale-up

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Abstract

Twin-screw granulation (TSG) offers a significant advantage over traditional granulation methods: the possibility of continuous manufacturing. Due to the recognized advantages of continuous manufacturing, TSG has drawn increased attention in recent years. This whitepaper summarizes the most important process parameters, their influence on product quality, and crucial parameters for scale-up based on a recent study. The results show that it is possible to tailor particle size distribution (PSD) of the granules, which enables scientists in pharmaceutical technology to influence final product quality right from the start. This whitepaper also summarizes valuable recommendations to address typical errors in designing, developing, and scaling up TSG. Consequently, TSG leads to faster process development and reliable scale-up from lab to production scale.

Introduction

Continuous manufacturing of pharmaceuticals has grown more popular in recent years.[1–6] There are several advantages of continuous processes over traditional batch processes:

1. The “batch size” is not a fixed value in continuous manufacturing. Therefore, especially in a drug’s research and development (R&D) phase, the amount of product can be reduced to the minimum needed for analysis and clinical trials. Furthermore, once the steady state has been reached, the product stream out of the extruder can be sampled and analyzed without needing to finalize the complete batch. This leads to fast conclusions and adaption and optimization of process parameters. Consequently, the design of experiment (DoE) and relevant tests, as well as small-scale production, take less time and less material in the R&D phase. Users of continuous processes report that up to 80% of time and material can be saved compared to a batch process. That makes continuous manufacturing quite valuable, especially when the active pharmaceutical ingredient (API) is only available in small quantities.
2. Once a continuous manufacturing line is set up, it can be operated in a very flexible way. Production volumes can be adapted to meet varying market demands; less storage space is needed for intermediate products, and less product is wasted because the amount can be tailored by process run time instead of the size of the equipment.
3. In continuous manufacturing, a constant process means constant product quality. Handling errors can be reduced more easily than with batch processes, and thus quality improves. Process analytical technology can also help to control process stability and ensure product quality. Essentially, with continuous manufacturing, only a limited amount of material is handled at a time rather than an entire batch. So if there is a problem with the process, the limited amount of current material can easily be discarded, and the process continues without interruption.

Based on the advantages above, many industries have already converted most of their processes to continuous manufacturing lines, e.g., polymer and food industries.

While pharmaceutical manufacturers are considering continuous manufacturing now, some of their processes are already inherently continuous, e.g., roller compaction, tableting, and hot melt extrusion (HME). HME is one of the most important techniques to produce solid dispersions for solid oral dosage forms, and several commercial drug products are currently produced with this technology.[7]

Based on HME, TSG has been developed as a continuous technique for granulation. The principle is shown in Figure 1. A solid powder is automatically fed into the twin-screw extruder. This can be done in a so-called split feed: feeding API and excipients separately or as a powder blend. A pump adds the liquid binder separately. The material is mixed, kneaded, and tempered within the barrel to a target temperature (via cooling or heating). Agglomeration takes place during this process.

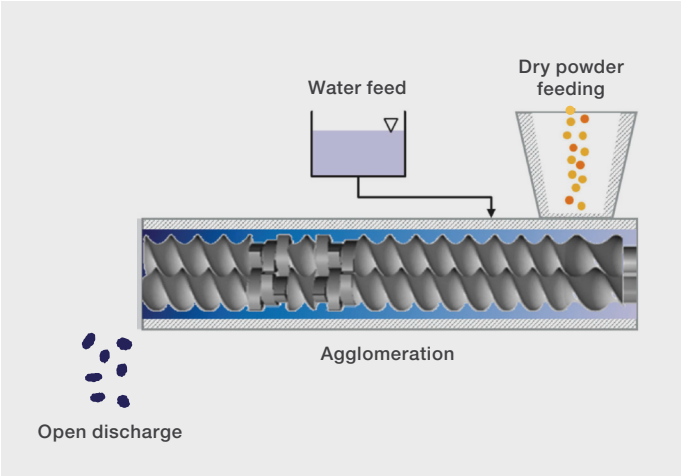

Figure 1: Schematic of a TSG process.

In contrast to extrusion, there is no die at the end of the barrel; thus, there is no pressure and no final compaction of the material. The granules exit the barrel through an open discharge and are transferred to the next process step (e.g., drying). There are several process parameters that can be changed independently:

- The liquid-to-solid ratio
- The total throughput of material that is fed into the barrel
- The screw speed of the extruder
- The screw configuration
- The temperature of the granulation process

These process parameters influence the granule quality, hence the final tablet hardness and the release profile of the API.

Several publications describe and analyze this process, showing its efficiency and potential for various drugs.[1, 3, 8–14] This white paper summarizes the influence of the most important process parameters.

In general, there are two ways to increase the amount of material produced via continuous manufacturing. First, the process can run for a longer time (at maximum throughput), and second, especially if time is a limiting factor, larger equipment can be used. The second possibility could require a scale-up from an R&D scale to a production scale, for example. Osorio et al. analyzed different scales of TSG processes resulting in a limited comparability of the granules.[15] While the scale-up approach is very straightforward, it's still critical to understand the key parameters involved in scale-up. This white paper shows a scalable process for a placebo formulation to help demonstrate the influence of key parameters.

Material and methods

In the study described in this white paper, granulation was performed on three different scales:

1. 11 mm with the Thermo Scientific™ Pharma 11 Benchtop Extruder (Figure 2A)
2. 16 mm with the Thermo Scientific Pharma 16 Extruder (Figure 2B)
3. 24 mm with the Thermo Scientific TSE 24 MC Twin-Screw Extruder.

The screw elements of these different instruments have diameters (D) of 11 mm, 16 mm, and 24 mm, respectively, and are shown in Figure 3. The extruders are geometrically comparable in terms of the similarity principle.16 This means that all sizes exhibit the same inner-to-outer diameter ratio and the same screw clearance ratio. Therefore, results obtained in one scale can be directly compared with other scales. In TSG mode, all screw lengths are 40 ¾ times the respective screw diameter.

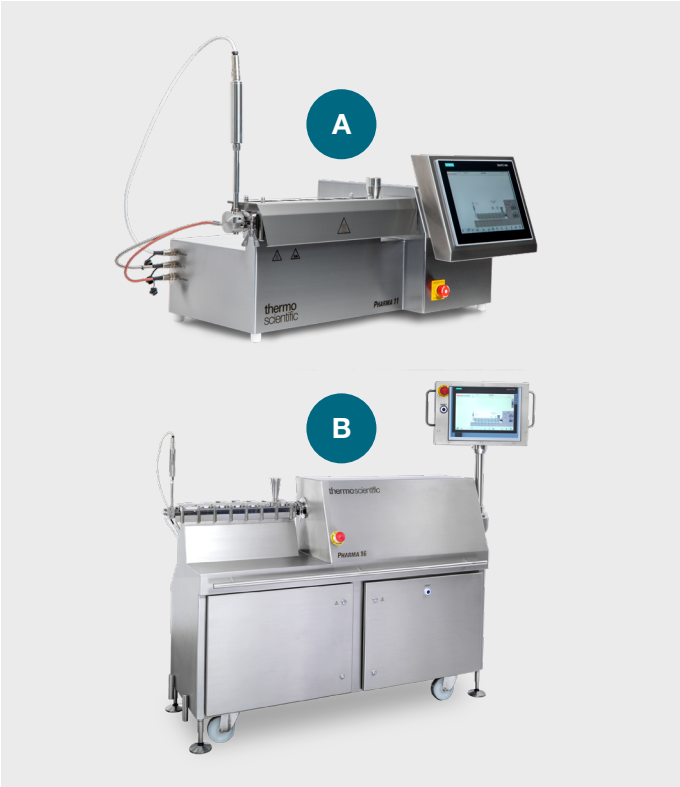

Figure 2: Pharma 11 Benchtop Twin-Screw Extruder (A); Pharma 16 Production Scale Twin-Screw Extruder (B).

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

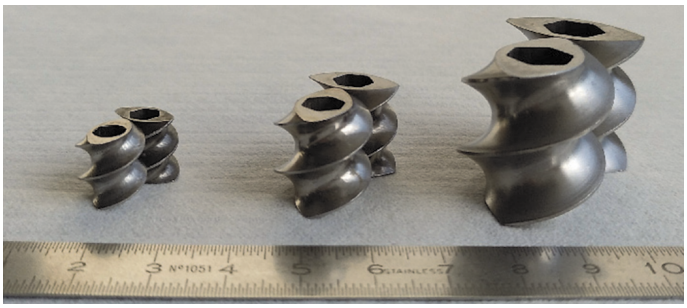

Figure 3: The three scales in this study: 11 mm, 16 mm, and 24 mm sized twin screws.

Results and discussion

The influence of TSG process parameters on the granule attributes (i.e., mass median diameter $d_{v,50}$, PSD and the granule density ρG) is summarized in Table 1. If the liquid-to-solid ratio is increased, the particles have a higher density and are larger (i.e., there are more oversize and fewer fine particles). This effect is the same as in other granulation methods and has been described before.[2, 17, 18]

A more interesting effect can be observed if the filling level of the screw is changed. This is mainly influenced by the total throughput and screw speed. An increase in throughput, for example, results in an increase of the filling level within the screws. Thus, stronger kneading and compaction are performed. In general, lower screw speeds and higher throughputs increase the filling level resulting in larger particles (see Figure 4). Based on this effect, the granules can be tailored more easily and quickly to the desired size. To obtain larger granules, for example, a higher throughput or a lower screw speed should be chosen. Furthermore, this effect should be considered for scale-out, i.e., reaching a higher throughput on the same scale should always incorporate an increase in screw speed.

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

Increase of process parameter	Effect on		
	$dV_{,50}$	PSD	ρ_G
Liquid-to-solid ratio	+	0	+
Throughput	+	+	+
Screw speed	–	–	–
Intensity of mixing (screw configuration)	+	0	+
Temperature	+	+	+

Note that the strength of the screw speed effect depends highly on the formulation and amount of binder (water). Figure 5 shows two curves of the mean particle size of the placebo formulation changing with the throughput. For a liquid-to-solid ratio of 25%, there is a strong dependency of the particle size on the throughput. An increase from 1 kg/h to 1.5 kg/h almost doubles the particle size. For a lower liquid-to-solid ratio (L/S), however, the particle size is almost independent from the throughput. Only at a throughput of above 3 kg/h does the mass median diameter of the granules increase significantly. These results are discussed in more detail in a dedicated lab report.[19]

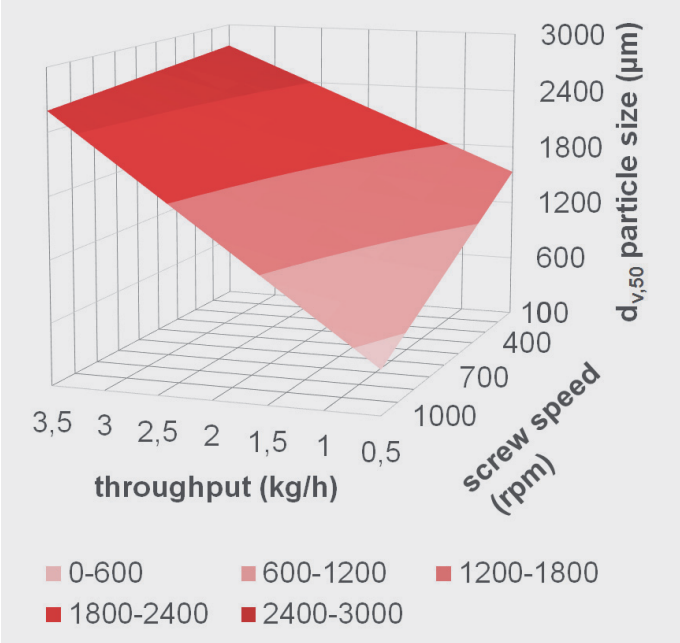

Figure 4: Surface plot of the mean particle size $d_{v,50}$) over throughput and screw speed. The data shown is an approximation of the determined size data in this study.

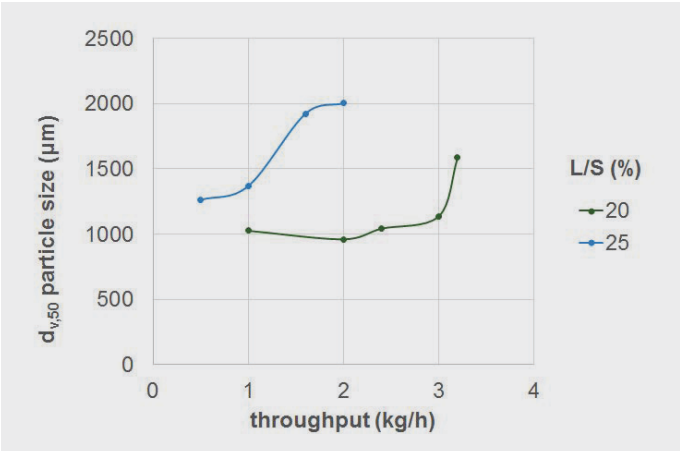

Figure 5: Influence of throughput and L/S on the mass median diameter ($d_{v,50}$) of the granules (Pharma 11 extruder, 500 rpm).

Consequently, the independent process parameters influence dependent parameters, e.g., the filling level of the screws. Thus, it is tempting to use this parameter (as a dimensionless number) to scale up this process.[15] But another dependent parameter needs to be taken into account: the residence time distribution (RTD) of the material inside the barrel. Figure 6 shows the mean residence time (MRT) of the material within the Pharma 16 extruder. MRT is defined as the time when 50% of the tracer leaves the barrel. It has been determined mathematically at 50% of the area below the tracer intensity curve. As can be seen in Figure 6, MRT decreases

with increasing screw speed for most throughputs. But at a very low throughput and high screw speed, a sharp increase of MRT is obtained. This is due to the low filling level of the screws resulting in a poor conveying behavior. That means a minimum filling level has to be reached to achieve an efficient process. An increase of particle size due to this mechanism has also been reported by Kumar et al.[20] and Seem et al.[1]

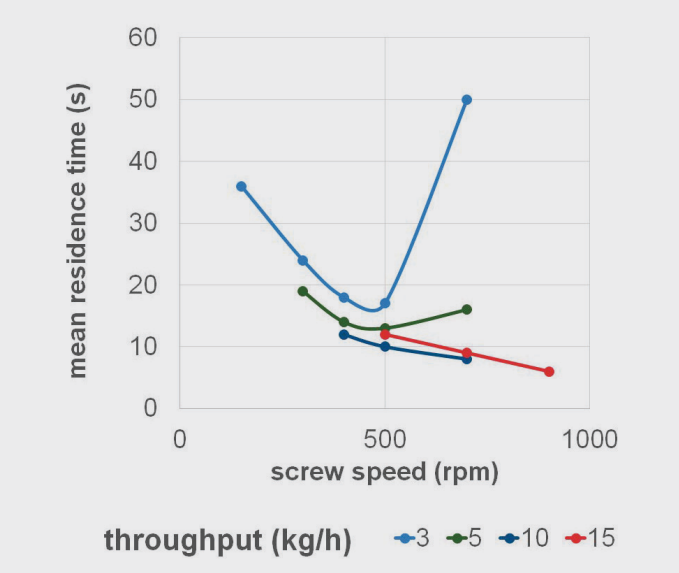

Figure 6: Mean residence time during granulation on the Pharma 16 Extruder.

Figure 7 summarizes the influence of throughput and screw speed on the mass median diameter of the granules made with the TSE 24. For a relatively high throughput (e.g., 40 kg/h), the mean particle size decreases with increasing screw speed as described before. But for a relatively small throughput (e.g., 5 kg/h), the opposite happens; the granules become larger with increasing screw speed. This is due to the strong decrease in the filling level and, thus, poor conveying behavior resulting in a wide RTD and a long MRT.

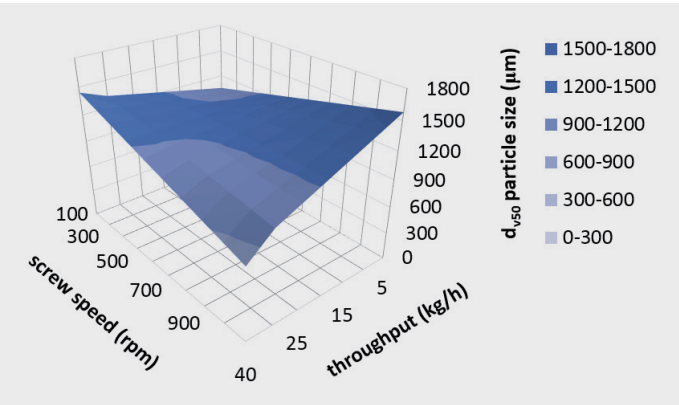

Figure 7: Influence of throughput and screw speed on the mass median diameter ($d_{v,50}$) of the granules (TSE 24). The data shown is an approximation of the determined size data in this study.

The final determination is that there are two main parameters that influence granule growth: compaction force depending on the filling level inside the screws and residence time within the extruder. Considering these effects and keeping all other parameters constant, the TSG process can be scaled-up successfully. To demonstrate this on different scales, Figure 8 shows the accumulated particle size of dry granules obtained on the Pharma 11 Extruder and the Pharma 16 Extruder.

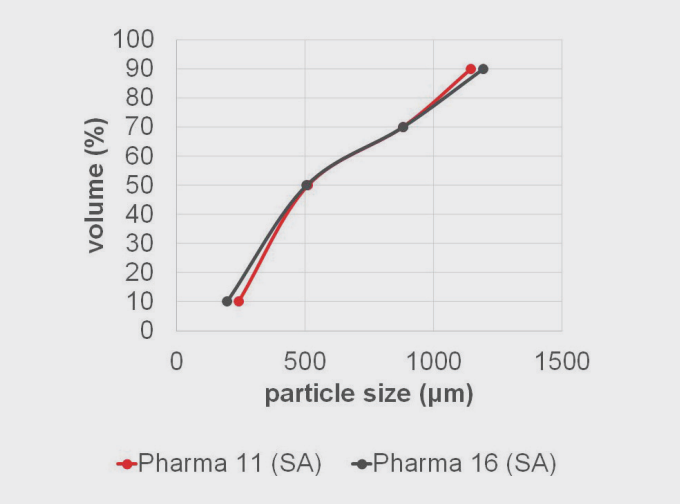

Figure 8: Particle size distribution from sieve analysis of granulates obtained on two different scales.

Typical errors in TSG

Based on the findings in this study and several publications, there are three typical errors to avoid in designing, developing, running, or scaling-up TSG processes.

1. **Working with a fixed screw configuration:** It really limits design space. Although not discussed in the present paper in depth, the screw configuration highly influences the granule quality.[10, 18] As shown by Meng et al., the influence of TSG process parameters on the granule quality can be quite limited if the screw is not changed.[14] A screw consisting of only soft mixing and kneading characteristics, for example, conveys the material very efficiently; thus, MRT is very low. This can lead to very poor granulation behavior for most process parameters. Therefore, the screw configuration needs to be adapted to the formulation.

2. **Inaccurate feeding of the solid or liquid materials into the extruder:** It leads to an inhomogeneous product. A twin-screw extruder has only limited back-mixing capability. This means that all material is conveyed as it enters the barrel. If this feed is not constant, the complete granulation process is not constant. This can result in a very wide or multimodal residence time distribution or granules with various densities. This effect has been well described by Meier et al.[12] Peristaltic pumps in particular tend to show a „dropping mode“ for very low feed rates. Working with multiple liquid injections, peristaltic pumps with two pump heads or with gravimetric pumps instead can solve this problem.

3. **Neglect of cooling power needed at different scales:** Particle size increases with higher temperatures caused by insufficient cooling. When scaling up a process, the amount of heat generated depends mainly on the mass or volume within the barrel (~D3). The heat transfer for cooling, on the other hand, is limited mainly by the surface area (~D2). Figure 9 shows the ratio of heat transfer area to volume plotted vs. the screw diameter. For small screw diameters, this ratio is very high resulting in an efficient cooling of the granulation process. But the ratio sharply decreases for larger screw diameters. This shows the importance of designing an adiabatic process or, if not possible, reducing the heat generation to a minimum, i.e., setting the screw speed and the intensity of kneading zones in the screw configuration as high as necessary but as low as possible.

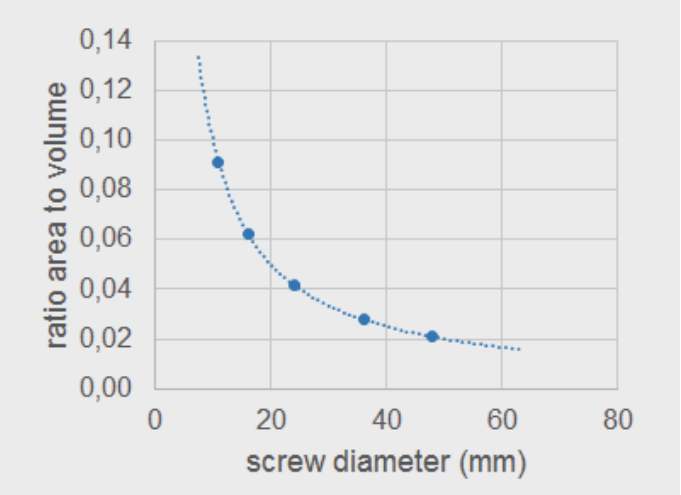

Figure 9: Ratio of heat transfer area to volume over screw diameter.

Paying special attention to the issues mentioned above can help to successfully implement continuous TSG in all phases of pharmaceutical manufacturing.

Conclusion

This white paper summarizes the most relevant parameters and provides a recommendation for process development and scale-up of a continuous TSG process. The summary explains how the PSD can be tailored to reach the desired product quality and API release profile on both an R&D scale and a production scale (see Figure 10).

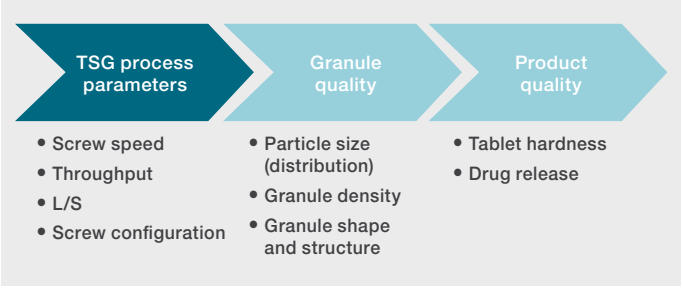

Figure 10: Schematic from tailor-made granules to optimal tablets.

The exemplary results show the importance of process understanding in continuous TSG. All process parameters (total throughput, liquid-to-solid ratio, screw speed, and barrel temperature), as well as the screw configuration, can significantly alter the granule quality. As a result, granule attributes can be tailored by changing the process parameters.

Extreme regimes (e.g., a very low filling level of the screws, a wide RTD, or a high L/S) can lead to non-linear dependencies with a strong influence on particle size and particle density. A scale-up in these regimes can be problematic as demonstrated in the results of Osorio et al.[5] Therefore, the relevant process parameters need to be determined for each formulation before scale-up. Filling level and residence time within the barrel need to be considered. Special attention needs to be drawn to determine the design space where the influence of process parameters is manageable. Scale-up can then be easily done with the resulting information. The granule quality produced on a small scale is predictive of granule quality generated at larger scales. This concept can also be seen in continuous wet granulation, including the drying process (Glatt® MODCOS xs-line, s-line, and m-line).

Acknowledgments

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References

1. T. C. Seem et al., “Twin screw granulation–A literature review,” Powder Technol., vol. 276, no. 815, pp. 89–102, 2015.
2. E. I. Keleb, A. Vermeire, C. Vervaet, and J. P. Remon, “Twin screw granulation as a simple and efficient tool for continuous wet granulation,” Int. J. Pharm., vol. 273, no. 1–2, pp. 183–194, 2004.
3. B. Van Melkebeke, C. Vervaet, and J. P. Remon, “Validation of a continuous granulation process using a twin-screw extruder,” Int. J. Pharm., vol. 356, no. 1–2, pp. 224–230, 2008.
4. S. Mascia et al., “End-to-end continuous manufacturing of pharmaceuticals: Integrated synthesis, purification, and final dosage formation,” Angew. Chemie–Int. Ed., vol. 52, no. 47, pp. 12359–12363, 2013.
5. M. Maniruzzaman, A. Nair, N. Scoutaris, M. S. A. Bradley, M. J. Snowden, and D. Douroumis, “One-step continuous extrusion process for the manufacturing of solid dispersions,” Int. J. Pharm., vol. 496, no. 1, pp. 42–51, 2015.
6. S. L. Lee et al., “Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production,” J. Pharm. Innov., vol. 10, no. 3, pp. 191–199, 2015.
7. R. M. Dhenge, J. J. Cartwright, D. G. Doughty, M. J. Hounslow, and A. D. Salman, “Twin screw wet granulation: Effect of powder feed rate,” Adv. Powder Technol., vol. 22, no. 2, pp. 162–166, 2011.
8. R. M. Dhenge, J. J. Cartwright, D. G. Doughty, M. J. Hounslow, and A. D. Salman, “Twin screw wet granulation: Effect of powder feed rate,” Adv. Powder Technol., vol. 22, no. 2, pp. 162–166, 2011.
9. D. Djuric, B. Van Melkebeke, P. Kleinebudde, J. P. Remon, and C. Vervaet, “Comparison of two twin-screw extruders for continuous granulation,” Eur. J. Pharm. Biopharm., vol. 71, no. 1, pp. 155–160, 2009.
10. D. Djuric and P. Kleinebudde, “Impact of screw elements on continuous granulation with a twin-screw extruder,” J. Pharm. Sci., vol. 97, no. 11, pp. 4934–4942, 2008.
11. A. Kumar et al., “Development of a process map: A step towards a regime map for steady-state high shear wet twin screw granulation,” Powder Technol., vol. 300, pp. 73–82, 2015.
12. R. Meier, M. Thommes, N. Rasenack, K. P. Moll, M. Krumme, and P. Kleinebudde, “Granule size distributions after twin-screw granulation–Do not forget the feeding systems,” Eur. J. Pharm. Biopharm., vol. 106, no. 815, pp. 59–69, 2016.
13. R. Meier, K. P. Moll, M. Krumme, and P. Kleinebudde, “Impact of fill-level in twin-screw granulation on critical quality attributes of granules and tablets,” Eur. J. Pharm. Biopharm., vol. 115, no. 815, pp. 102–112, 2017.
14. W. Meng et al., “Statistical analysis and comparison of a continuous high shear granulator with a twin screw granulator: Effect of process parameters on critical granule attributes and granulation mechanisms,” Int. J. Pharm., vol. 513, no. 1–2, pp. 357–375, 2016.
15. J. G. Osorio et al., “Scaling of continuous twin screw wet granulation,” AIChE J., no. 815, 2016.
16. W. Schuler, “Hochrechnung von Versuchs-auf Produktionsextruder,” in Der Doppelschneckenextruder–Grundlagen und Anwendungsgebiete, 1998.
17. P. Beer, D. Wilson, Z. Huang, and M. De Matas, “Transfer from high-shear batch to continuous twin screw wet granulation: A case study in understanding the relationship between process parameters and product quality attributes,” J. Pharm. Sci., vol. 103, no. 10, pp. 3075–3082, 2014.
18. P. Beer, D. Wilson, Z. Huang, and M. De Matas, “Transfer from high-shear batch to continuous twin-screw wet granulation: A case study in understanding the relationship between process parameters and product quality attributes,” J. Pharm. Sci., vol. 103, no. 10, pp. 3075–3082, 2014.
19. M. Richter and C. O’Callaghan, “Unique Advantages of Process Analytical Technology in Twin-Screw Granulation,” Lab report, Karlsruhe, Germany, 2017.
20. A. Kumar et al., “Mixing and transport during pharmaceutical twin-screw wet granulation: Experimental analysis via chemical imaging,” Eur. J. Pharm. Biopharm., vol. 87, no. 2, pp. 279–289, 2014.

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