APPLICATION NOTE

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# Dry granulation as a twin-screw process in pharmaceutical applications

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## Introduction

Two different processes can be performed using parallel co-rotating twin-screws (see Fig. 1): If a die is placed at the end of an extruder barrel, and material is compacted and pressed pressed through this die, then the process is called extrusion. By omitting the die the material can be kneaded and agglomerated in the barrel without an increase in pressure. This process is called granulation. Both processes can be performed with and without water.

Wet granulation is a standard process for many solid dosage forms. Here, water is used as a binder to agglomerate smaller particles. This requires a drying step after granulation process. Some active pharmaceutical ingredients (API), however, are very sensitive to hydration or to heat, requiring alternative granulation techniques be investigated. Dry granulation requires high mechanical forces for compaction. Using a thermoplastic binder however, thermally activated dry granulation can be performed on parallel twin-screws [1]. Then, the drying step is not needed.

In comparison to hot melt extrusion (HME) dry granulation is performed above the glass transition temperature of the polymeric binder, but below the melting temperature of the API [2]. Furthermore, in case of dry granulation low binder contents of approx. 10% can be used, allowing the production of high-dose formulations.

## Materials and Methods

In this report dry granulation is tested using the Thermo Scientific™ Pharma 11 Twin-Screw Extruder with the granulation kit and a gravimetric Twin Screw feeder by Brabender Technology. The set-up and the used screw configuration are shown in Fig. 2 and Fig. 3 respectively.

Two different formulations are analyzed, which mainly differ in the used binder (see Table 1). The first binder, Kollidon® VA64 exhibits a glass transition temperature $T_g$ of 105 °C.

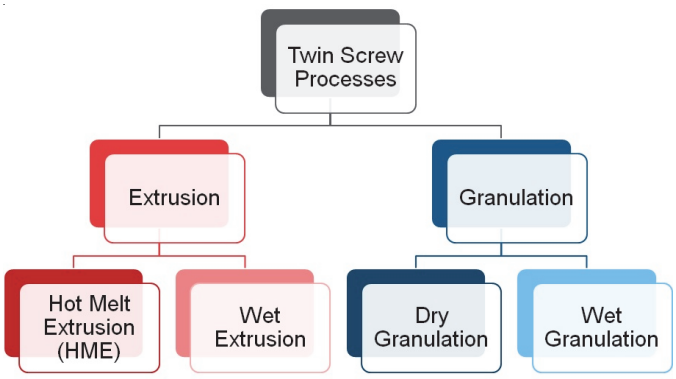



**Fig. 1:** Overview of twin-screw processes.

Monteyne et al. showed that granulation temperatures below the glass transition temperature are possible [3]. Therefore, the temperature for twin-screw granulation $T_{TSG}$ was varied between 30 °C and 50 °C. To start granulation in the twin-screw extruder the barrel needs to be quite full. Therefore, Trial I was performed at a throughput between 1.5 kg/h and 2.0 kg/h. The granulation was started with a screw speed of 150 rpm. As the polymer (binder) starts to plasticize, and the product starts to compact in the mixing zone, the extruder torque is going up. By increasing the screw speed from 150 rpm to 300 rpm, the filling level of the extruder can be reduced, which avoids an overload of the extruder.

In Trial II the binder Soluplus® (BASF) with a lower glass transition temperature was chosen. Furthermore, the process temperature was raised to 130 °C or 150 °C. In Trial II lower throughputs and screw speeds are realized. A sieve analysis was performed for the resulting materials. Lactose was used a as a substitute for an API in both formulation trials.


**Fig. 2:** Process set-up for dry granulation: Pharma 11 Twin-Screw Extruder with granulation kit.

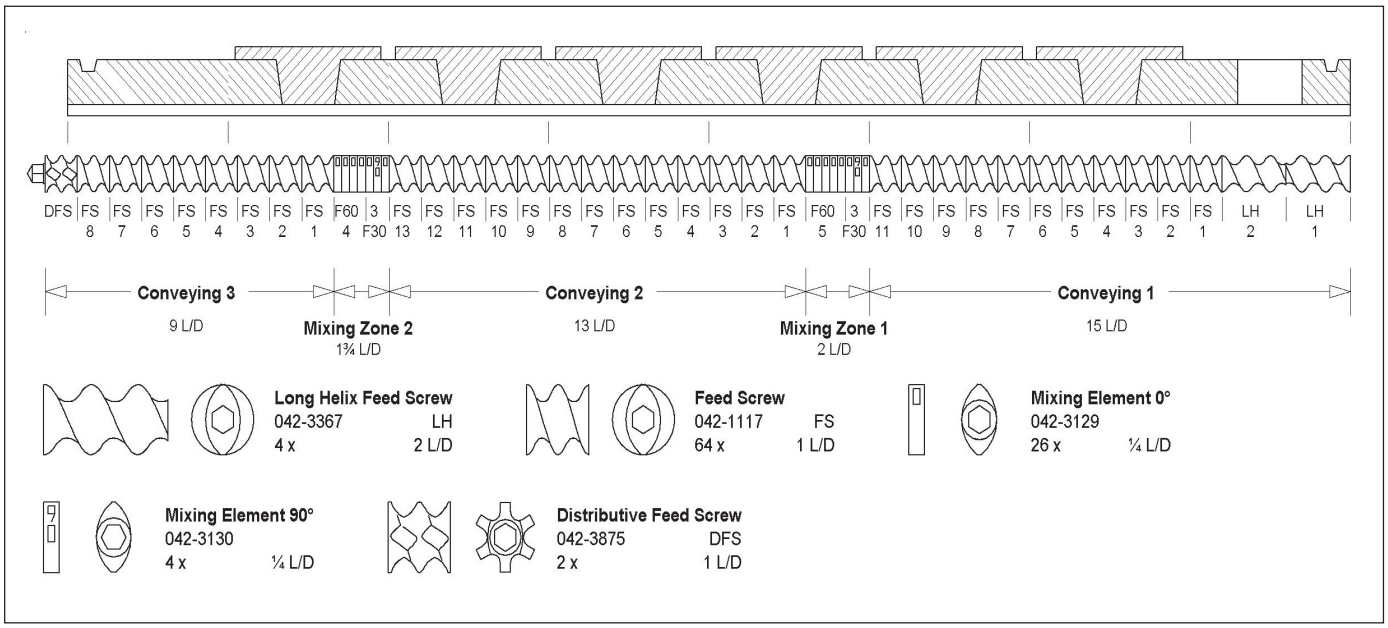



**Fig. 3:** Screw configuration for dry granulation.

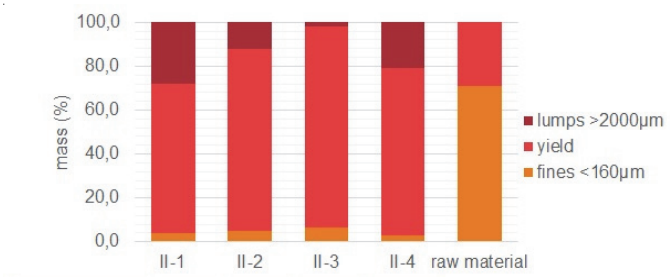
## Table 1: Formulations and process parameters

| | Trial I | Trial II |
|---|---|---|
| Formulation | 15% Kollidon® VA64<br>5% MCC<br>in lactose | 15% Soluplus®<br>in lactose |
| $T_g$ (binder) | 105 °C | 72 °C |
| $T_{TSG}$ | 30-50 °C | 130 °C<br>150 °C |
| Feed rate | 15-2 kg/h | 0.5 kg/h |
| Screw speed | 150-300 rpm | 70-130 rpm |

## Results

A torque of 75% to 90% of the maximum torque was reached during granulation in Trial I. Consequently, the material heated up in the extruder barrel mixing zones, resulting in an unstable process under these conditions. It is known that a suitable temperature for the dry granulation process not only depends on the polymeric binder, but also on the API [2]. In the trials described here lactose is used as a substitute for an API. As a result, the very high melting temperature of lactose might limit the suitable granulation temperature. As stated by Batra et al. it is essential to run the process above the glass transition of the polymer [2]. Therefore, in Trial II the process conditions have been changed resulting in a stable process. Fig. 4 summarizes the results from sieve analysis for the different process conditions indicated in the table (Trial II-1 to II-4). The right-hand side of the graph shows that the raw material consists of mostly fine particles (smaller than 160 µm). All samples from Trial II show an increase in particle size, resulting in at least 70% yield-size particles. In experiments II-1 to II-3 the screw speed was varied, showing that the particle size distribution is very sensitive to this parameter. For wet granulation an increase in screw speed normally results in a decrease in overall particle size, reduction of oversized particles and a narrower particle size distribution [4]. In the present experiments for dry granulation this trend is not clear. Increasing the screw speed from 100 rpm to 130 rpm (see II-1 and II-3 in Fig. 4) does increase the yield due to reduction of oversize particles on the one hand. But on the other hand a decrease to 70 rpm seems to have the same effect. This result needs further analysis.

A change in barrel temperature from 150 °C to 130 °C (II-3 and II-4) results in a larger amount of oversize particles and less fines. This can be explained by the increase of viscosity of the polymeric binder. The resulting torque during the granulation seems to be a good indicator for the quality of the process. Experiment II-1 and II-4 exhibited the same torque and a similar particle size distribution.




| | | | | |
|---|---|---|---|---|
| T (°C) | 150 | 150 | 150 | 130 |
| screw speed (rpm) | 100 | 70 | 130 | 130 |
| torque (%) | 50 | 70 | 38 | 50 |

**Fig. 4:** Results of sieve analysis from Trial II.

## Conclusions

Dry granulation is a viable process for pharmaceutical applications as hydration of the API can be prevented and the thermal stress reduced. By adding at least 10% polymeric binder to the API the particle size can be increased (see Fig. 5) in order to improve flowability, avoid segregation, reduce dust formation and ease compaction in tablet pressing.

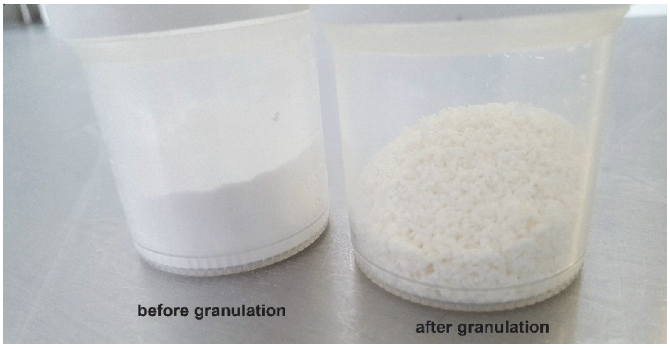



**Fig. 5:** Material before and after dry granulation.

The resulting torque in the dry granulation processes tested here proved to be an important indicator of process stability, especially compared to wet granulation where the torque barely increases during the process. The filling level influenced by feeding rate and screw speed has a high influence on the dry granulation. On the one hand at a very low filling level no granulation is possible. The material is simply conveyed through the screws. On the other hand a very high filling level might result in the blockage of the screws and triggered a torque alarm. This effect can also be induced at very low process temperatures. The appropriate granulation temperature $T_{TSG}$ must be determined for each formulation since this parameter depends on the interaction and properties of the API and the binder.

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## References


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