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Original Research Paper

Is the adjustment of the impeller speed a reliable attempt to influence granule size in continuous dry granulation?

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ABSTRACT

As the field of continuous manufacturing of solid pharmaceutics is developing, the interest in implementing continuous granulation methods is growing. Process analytical technology tools should be integrated to ensure the monitoring of the product quality and therefore enforce control strategies.

Three single materials which are often used in dry granulation and additionally two formulations, one containing ibuprofen and the other acetaminophen were processed at various process parameters. They all differed in their compaction and fracture behavior. A statistical analysis of the influence of process parameters was executed, to work out which parameters could be used for a granule size control approach in continuous dry granulation. Thereby, the specific compaction force and the impeller speed were found to be significant factors in each design of experiment. However, the impeller speed was evaluated as the only suitable parameter to control granule size, as an impact on granule density is unlikely. Nevertheless, some restrictions such as an upper impeller speed limitation to avoid excessive fines and a lower speed limitation to impede a downturn of the throughput, have to be considered. Furthermore, a decreasing median granule size was observed at higher throughputs for plastically deforming materials and formulations.

1. Introduction

Continuous manufacturing of solid pharmaceuticals has recently moved into the focus of pharmaceutical research. First products are registered and it appears to further continue as an orientation since this way of manufacturing comes with a lot of benefits [1–3].

To manufacture tablets from different materials in a continuous process, it is necessary to have different processing routes accessible. The easiest way is presented by continuous direct compression [4]. Usually, several gravimetric feeders are feeding into a continuous blending unit. Subsequently, the powder blend is fed into the tablet press, which works continuously by definition. The number of processes, which are connected with each other are manageable. As in batch production, not every product is suitable for direct compression, particularly due to the lack of flowability. A common way to increase flowability is to enlarge the particle size, which also benefits other characteristics, such as homogeneity and segregation of a mixture. Therefore, particle size enlargement is a key element in the production of solid pharmaceuticals.

The methods for particle size enlargement in continuous manufacturing are focused on twin-screw granulation in the case of wet granulation, whilst for dry granulation roll compaction is the method of choice [5,6]. Both processes are continuous by definition. The integration of these processes into a continuous manufacturing line makes the whole process more complicated. Consequently, a series of additional process analytical technology (PAT) tools are needed to monitor and control the process.

This study sheds light on dry granulation and its applicability in a continuous manufacturing line. More specifically, the way to influence the final product quality attributes is discussed.

Dry granulation is usually conducted with a roll compactor. There are different roll compactors commercially available. These are all following the identical main principle, but they can be different in their setup. During processing, the powder is densified through being fed between two counter rotating rolls [7]. The emerging ribbons, as intermediates, are subsequently broken down to the granules. The granule forming process is strongly dependent on the material properties, ribbon density and the process equipment. Particularly the granulation unit configuration significantly contributes to the process. Numerous parameters can be altered, which influence the product quality. Here, PAT tools have to be implemented. PAT tools should monitor the product quality

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continuously in the process. A product has to be discharged in case of an out-of-specification event, which is detected by the PAT tools when the quality is beyond the predefined design space. In case of such a dischargement out of the production line, up-stream processes have to increase their individual throughput in order to achieve a pursued production rate at the end of the process.

Great efforts with good attainments are already done in monitoring the ribbon density with NIR [8] and thermographic methods [9]. PAT tools for in-line particle size measurements, were discussed several times, however, an implementation is reported rarely for dry granulation [10]. Singh et al. [11] proposed a strategy about the way to control particle size in continuous roll compaction/dry granulation. It is claimed that changing the milling speed (impeller speed) can be used to control the size of the granules in the process. On the basis of the deviation between the desired granule size distribution (GSD) and the actual GSD, measured with a PAT tool an error is calculated. This error enters a PID control law to set a new control variable for the mill speed (impeller speed) (Fig. 1).

This study reviews the claim to control granule size by adjusting the impeller speed of the granulation equipment. For this purpose, batch experiments with different process parameters were performed with a particular focus on the impeller speed of the granulation unit. These batch experiments allow to draw conclusions for continuous processing. Different materials and formulations were reviewed in regard to their granule size distribution of after roll compaction / dry granulation and were linked to their compression/fracture behavior. As throughput is a major concern in continuous processing, it was also taken into consideration. Throughput changes could be necessary, e.g. by discharging out-of-specification product and increasing the production speed of up-stream processes to keep a certain desired throughput.

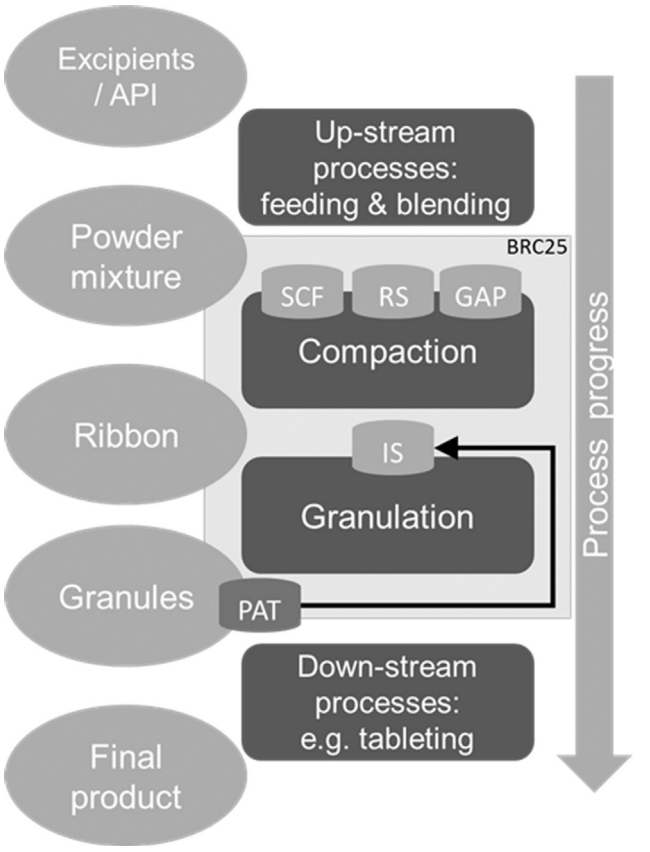

Fig. 1. Scheme of the process, black arrow symbolizes a feedback control (PID). Specific compaction force (SCF), roll speed (RS), impeller speed (IS).

2. Experimental

2.1. Materials

Various materials with different compaction behavior were chosen. Microcrystalline cellulose MCC (Vivapur 102, JRS, Germany), a co-processed microcrystalline cellulose MCCDG (Avicel DG, FMC Biopolymer, USA) and a coarse grade of dibasic calcium phosphate anhydrate DCPA (Di-Cafos A150, Budenheim, Germany) were chosen as model excipients to evaluate the change in particle size by processing with different process parameters. Furthermore, two different formulations with four components and a high drug load (Table 1) were processed to check if findings could be applied to different formulations. Acetaminophen (APAP, Paracetamol Ph.Eur./USP extra fine powder, Atabay, Turkey) and ibuprofen (IBP, Ibuprofen 50, BASF, Germany) were chosen as model drugs. The active pharmaceutical ingredients were mixed with hydroxypropyl cellulose (HPC, HPC SSL SFP, Nippon Soda, Japan) as binder, croscarmellose sodium (XCS, Vivasol, JRS, Germany or Ac-Di-Sol SD-711, FMC, USA) as disintegrant and DCPA or mannitol (Pearlitol 200SD, Roquette, France) as filler.

2.2. Powder preparation

For experiments with a single material, it was used as supplied. For experiments with formulations, APIs and binder were sieved using a mesh size of 355 μm to avoid larger agglomerates. The physical mixtures were blended in a container mixer (LM40, L.B. Bohle, Germany) for 20 min at a rotation speed of 20 rpm. The batch size was 7 kg for Formulation 1 and 10 kg for Formulation 2.

2.3. Compression analysis

A compaction simulator (Styl'One Evolution, MedelPharm, France) with force feeding was used for compression analysis. Flat faced tablets with a diameter of 8 mm and a target weight of 200 mg were produced. All materials were compressed with a compaction pressure of approximately 250 MPa. The densities to perform Heckel-analysis [12] were obtained by helium pycnometry (AccuPyc 1330, Micromeretics, USA). The linear part of the ascending curve was used for this analysis. Thereby, the mean yield pressure was automatically obtained from the slope of the linear part of the ascending curve.

2.4. Roll compaction/dry granulation

An instrumented roll compactor (BRC25, L. B. Bohle, Germany) was used for dry granulation. The compaction unit was equipped with smooth rolls and a rim roll sealing. Process parameters and process equipment were adjusted to each material (Table 2). The granulation unit was equipped with a conical rasp sieve of different mesh sizes with a rotating, in work direction bent two blade-impeller. The ribbons are shredded to granules in the granulation unit.

2.5. Throughput

The throughput was measured with a balance (Sartorius, Germany), which was connected to a PC containing a software that tagged the weight each 10 s. The balance was located directly at the output of the granulation unit of the compactor (Fig. 2). Samples were taken, once the differential balance values were

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