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Research paper

Impact of fill-level in twin-screw granulation on critical quality attributes of granules and tablets

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ABSTRACT

In a previous study a change of the fill-level in the barrel exerted a huge influence on the twin-screw granulation (TSG) process of a high drug loaded, simplified formulation. The present work investigated this influence systematically. The specific feed load (SFL) indicating the mass per revolution as surrogate parameter for the fill-level was applied and the correlation to the real volumetric fill level of an extruder could be demonstrated by a newly developed method. A design of experiments was conducted to examine the combined influence of SFL and screw speed on the process and on critical quality attributes of granules and tablets. The same formulation was granulated at constant liquid level with the same screw configuration and led to distinctively different results by only changing the fill-level and the screw speed. The power consumption of the extruder increased at higher SFLs with hardly any influence of screw speed. At low SFL the median residence time was mainly fill-level dependent and at higher SFL mainly screw speed dependent. Optimal values for the product characteristics were found at medium values for the SFL. Granule size distributions shifted from mono-modal and narrow shape to broader and even bimodal distributions of larger median granule sizes, when exceeding or falling below a certain fill-level. Deviating from the optimum fill-level, tensile strength of tablets decreased by about 25% and disintegration times of tablets increased for more than one third. At low fill-levels, material accumulation in front of the kneading zone was detected by pressure measurements and was assumed to be responsible for the unfavored product performance. At high fill-levels, granule consolidation due to higher propensity of contact with the result of higher material temperature was accounted for inferior product performance. The fill-level was found to be an important factor in assessment and development of twin-screw granulation processes as it impacted process and product attributes enormously.

1. Introduction

Triggered by the Food and Drug Administration's guidance regarding process analytical technologies (PAT) in 2004 [1], a paradigm change in the pharmaceutical industry towards the continuous production of pharmaceuticals has commended. A major implication of continuous processing is the necessity of extensive and real-time knowledge of process and material attributes in the framework of quality by design. Critical process parameters (CPP) and critical quality attributes (CQA) have to be defined and monitored as consistently as possible to ensure constant and homogenous product quality. Furthermore, the traceability of all ingredients of a pharmaceutical formulation throughout the process up to the point of the finished product has to be secured. One approach to reduce the complexity of this real-time and traceability analysis in case of continuous twin-screw granulation (TSG) was the introduction of simplified formulations, which contained beside the active pharmaceutical ingredient (API) as few excipients as possible. These simplified formulations were investigated for mechanically different behaving drugs (plastic and brittle) and contained only API and disintegrant or API, disintegrant and binder [2,3]. Depending on the applied API, different disintegrants could be used to ensure fast disintegration and strong tablets. In addition to the reduction of traceability problems and the complexity of

Abbreviations: API, active pharmaceutical ingredient; CPP, critical process parameter; CQA, critical quality attribute; D, diameter of the extruder screws; DOE, design of experiments; GSD, granule size distribution; IQR, interquartile range; L/S-ratio, liquid to solid ratio; MRT, median residence time; PAT, process analytical technology; SFL, specific feed load; SS, screw speed; TSG, twin-screw granulation; x_{50}, median granule size.

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real-time analysis, the formulations get less susceptible to batch inconformities, which can arise with natural, semi-synthetic and fully synthetic products.

During the development of simplified formulations with the API hydrochlorothiazide and the disintegrant sodium starch glycolate, some problems encountered [3]: a pulsating output of the extruder, characterized by oscillating intervals of high output following intervals of low output. Furthermore, at different time points of the process differently sized granules left the extruder. An accumulation of material in front of the kneading zone was supposed to be responsible for the problems. It was hypothesized that the accumulation was cleared as soon as new material produced enough pressure to convey the material through the kneading zone. The problems could be solved by an increase of the throughput keeping all other process parameters constant. Alongside with the process improvements, CQAs of the granules and tablets could be improved. Effectively, by increasing the throughput, the fill-level of the extruder was elevated.

The volumetric fill-level of an extruder is the volume, the material occupies, in proportion to the maximum available volume in the extruder barrel. There are plenty of studies published, which dealt indirectly with the fill-level in TSG or in which the fill-level was influenced indirectly [4–11]. However, in none of these studies, the fill-level was determined or directly and systematically investigated as independent factor. This is because the volumetric fill-level of an extruder cannot be adjusted readily due to several unknown variables. A method, applied by the research group of Thompson [12–14], called screw pullout would come closest to determine the volumetric-fill degree, but thereby still not the whole material would be captured. But as the volumetric fill-level of an extruder is mainly determined by the throughput and the screw speed (SS) as input and output determining variables, a preliminary surrogate parameter for the volumetric fill-level will be employed in this study. Literature about extrusion provides two rather similar parameters, namely the specific feed load (SFL). Kolter et al. [15] defined it according to Eq. (1) as gravimetric mass flow divided by the screw speed, which results in a mass, which is transported per screw revolution, with the dimension of mass [g]. Kohlgrüber [16] defined it similarly with a further multiplication by the screw diameter and the material density in the denominator, resulting in a dimensionless number. In the context of this study it was decided to employ the SFL, according to Kolter et al. [15], because of its simplicity. However, it has to be mentioned that the SFL is only valid for one applied system, meaning the formulation, the extruder dimensions and the screw configuration, because in both equations the maximum capable volume of the extruder is not included.

$$SFL = \frac{\dot{m}}{f} \quad (1)$$

SFL: specific feed load [g],
$\dot{m}$: gravimetric throughput [g/min],
f: screw speed [1/min].

The aim of this study was to investigate if the SFL correlates with the volumetric fill-level of an extruder and if it is justified to use it as surrogate parameter. Therefore, a preferably simple method to measure the volumetric fill-level of an extruder had to be developed. With this knowledge a design of experiments (DOE) with the SFL as independent factor and the problematic formulation from the prior study [3] should be conducted, whereby the influence of the SFL on process parameters and CQAs should be investigated. At last, the hypothesis of the pressure built up through material accumulation in front of the kneading zone at low SFL should be assessed.

2. Materials and methods

2.1. Materials

The applied formulation consisted of 89.8% (w/w) hydrochlorothiazide (Unichem Laboratories, Mumbai, India), 10% sodium starch glycolate (Explotab, JRS Pharma, Rosenberg, Germany) and 0.2% colloidal silica (Aerosil 200, Evonik, Darmstadt, Germany). Demineralized water was used as granulation liquid. During the residence time determinations, the red dye Sicovit Amaranth 85 E 123 (BASF, Ludwigshafen, Germany) was used as tracer substance. For the tableting experiments, magnesium stearate (Parteck LUB MST, Merck Millipore, Darmstadt, Germany) was used as lubricant.

2.2. Methods

2.2.1. Design of experiments

To investigate the influence of the SFL (low level: 0.15 g, high level: 0.4 g) and the SS (low level: 200 1/min, high level: 500 1/min) on the process and on CQAs of granules and tablets, a central composite design was planned, to allow the evaluation of linear and quadratic effects, as well as interactions of the factors. This design consisted of a two level full factorial design with three executions of the center point experiment, resulting in seven trials. Additionally, four star points were added as trials, with a star distance of 1.414 (square root of two), from the center point in each direction of the factors. Three additional trials at different SFLs were added to the experimental plan, resulting in a total of 14 experiments. The sequence of the trials was randomized, to minimize the effect of unknown, systematic influences. A complete overview of the experiments and the different factor settings is given in Table 1. Following response variables were evaluated: volumetric fill-level [%], median granule size [μm], granulation yield (granules from 180 μm to 1000 μm) [%], amount of oversized granules (>1700 μm) [%], disintegration time of tablets [s], tensile strength of tablets [MPa], power consumption of the extruder [%], median residence time of material inside the extruder [s], material temperature in front of 2nd kneading zone [°C]. The DOE was planned and evaluated with the software Modde 9.0 (Umetrics, Umeå, Sweden) using multiple linear regression at a significance level of $\alpha = 0.05$. After fitting to the experimental data, the model for each response was refined via backwards regression to result in the highest possible value for the coefficient of prediction (Q^2).

2.2.2. Preparation of powder mixtures

Powder amounts of 5 kg each were blended for 20 min in a laboratory scale blender at 35 1/min (LM 40, L.B. Bohle, Ennigerloh, Germany).

2.2.3. Twin-screw granulation and drying

After mixing, powder was transferred to a gravimetric powder feeder (K-ML KT20, K-Tron, Niederlenz, Switzerland), which fed the powder at the desired fee-rate, according to the experimental plan. Granulation liquid of 25 °C was fed through a nozzle of 0.12 mm inner diameter directly on the top of one screw, in front of the first kneading zone. The applied pump was a micro annular gear pump (MZP 7205, HNP-Mikrosysteme, Schwerin, Germany), which was monitored and manually controlled by a Coriolis mass flow meter (Proline Promass 80A, Endress + Hauser, Weil am Rhein, Germany). The liquid to solid ratio (L/S) was kept constant throughout all experiments at 0.11. Granulation was performed on a twin-screw extruder (Pharmalab 16, Thermo Fisher Scientific, Karlsruhe, Germany), which had a screw diameter (D) of 16 mm