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Optimizing feed frame design and tableting process parameters to increase die-filling uniformity on a high-speed rotary tablet press

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ABSTRACT

Despite the high quantities of tablets produced daily, many tableting processes are still operated at sub-optimal settings and hence lack the necessary flexibility to mitigate for possible process deviations. However, to ensure this flexibility on tableting throughput it is important to select the most robust feed frame design and settings regarding die-filling. In this research study, four paddle designs for a two-compartment forced feeder (equipped with a metering and a feeding paddle wheel) were evaluated at a wide range of process-settings (i.e. tableting speed, paddle speed, overfill level) and feed frame features (i.e. deaeration) for their impact on the die-filling step of a poorly flowing model formulation (i.e. MCC 101) using a quality-by-design approach. No benefit on die-filling was observed when using higher speeds of the metering paddle wheel compared to the feeding paddle wheel, and no convincing arguments were obtained to use the feed frame deaeration opening. Some combinations of paddle design and process-settings significantly increased the risk for inconsistent die-filling (i.e. high tablet weight variability) which can therefore limit the efficiency of the tableting process. The approach used in this study enabled to compare the paddle designs for their die-filling performance in function of varying tableting speeds, eventually resulting in the selection of a feed frame design that is most robust and therefore will provide a uniform die-filling over a wide range of throughputs. Selection of the most robust parameters is an important prerequisite for the ability of using the rotary tablet press as an agile unit-operation.

1. Introduction

Powder compression on rotary tablet presses is widespread in various industries, which is clearly reflected in pharmaceuticals where tablets are by far the most popular dosage form. The ease of manufacturing combined with a high economic efficiency, high accuracy of dosing and patient convenience all contribute to the dominance of tablets (Armstrong, 2007). Die-filling can be considered as a crucial control variable of the tableting process since it is critical for obtaining the desired tablet weight and hence drug dose, but also less obvious quality attributes such as size, tensile strength and drug release are (in) directly affected by this step (Armstrong, 2007; Mateo-Ortiz and Méndez, 2015; Sinka et al., 2009; Xie and Puri, 2006). Moreover, die-filling can be rate-limiting for the tableting process and therefore impact the throughput of the entire continuous line when the tablets press in linked to other unit-operations.

With the pharmaceutical industry gradually shifting towards continuous manufacturing, the use of a rotary tablet press in continuous manufacturing lines is often considered because of its inherently continuous nature (Byrn et al., 2015). While a tablet press in batch processing is mainly operated at a constant throughput, this operation mode could create problems in a continuous production line (e.g. material holdup at the tablet press or needing to shut down the press) if mass flow variation occurs in the upstream unit operations of the line (Martinetz et al., 2017). Ideally, each unit operation should be able to adapt to changes in throughput without negatively impacting the

Abbreviations: API, active pharmaceutical ingredient; CP, centerpoint; CQA, critical quality attribute; DOE, design of experiments; MBPH, main-compression bottom punch height; MCC, microcrystalline cellulose; MCD, main-compression displacement; MCF, main compression force; MLR, multiple linear regression; Pa1, feeding paddle wheel (1); Pa2, metering paddle wheel (2); PBPH, pre-compression bottom punch height; PC, principal component; PCA, principal component analysis; PCD, pre-compression displacement; PCF, pre-compression force; QbD, quality-by-design; RSD, residual standard deviation; s, seconds; TH, tablet hardness; TW, tablet weight

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quality of intermediates or final products. Martinetz et al. recently introduced an interesting concept to step away from the conventional view of the rotary tablet press as the so called “master” in a control concept since it defined the mass flow through the entire process by operating at constant turret speed. They proposed an operation concept which introduces flexibility in the process to handle upstream mass flow fluctuations by modulating the press turret speed in function of the hopper fill level and hence adjusting the mass flow rate into and from the tablet press (Martinetz et al., 2017). This concept was verified for good flowing mixtures and proved that the tablets critical quality attributes (CQAs) were not significantly affected within the proposed design space.

However, it is generally recognized that higher turret speeds have a negative impact on the die filling step, especially when poorly flowing powders are used (Mendez et al., 2010; Yaginuma et al., 2007). Pharmaceutical powders often lack sufficient flow properties and flowability of powders is often the rate limiting step during die-filling. In most high-speed rotary tablet presses, feed frames are used to facilitate filling of the die-cavities with powder. During this die-filling step, various mechanisms (i.e. gravity feeding, forced feeding, suction fill, overhead pressure, centrifugal forces, air pressure and vibrations) act simultaneously (Jackson et al., 2007; Peeters et al., 2015; Schneider et al., 2007; Sinka et al., 2004). Particularly poorly flowing powders are more subjected to forced feeding than gravity feeding and hence it is expected that the feed frame design will play a major role in the die-filling step of these challenging formulations (Mendez et al., 2010; Peeters et al., 2015; Sun, 2010). A deliberately selected, robust paddle design for the feed frame could guarantee a uniform die-filling step for such formulations at fluctuating turret speeds when the rotary tablet press is used as agile unit-operation in a continuous manufacturing line.

Although a wide variety of feed frames which differ in number of compartments, paddle-design and volume are currently available, up till now there is only limited public knowledge on when and how to use a specific design at its most suitable process settings to obtain the best tablet quality. This explains the rather paradoxical situation that many companies and institutions currently face: despite the fact that tablets are already produced for decades, the established tableting process are still too often based on trial-and-error or ‘in-house’ knowledge and many tablet presses are operated at sub-optimal settings.

The aim of this research paper is therefore to provide in-depth knowledge on the various paddle-designs of a two-compartment forced feeder and their impact on the die-filling step of a rotary tablet press under realistic process-settings. This knowledge could contribute to an improved set-up of industrial tableting processes by choosing the most robust feed frame design for a wide range of tableting process-settings.

2. Materials and methods

Microcrystalline cellulose (Vivapur® 101, JRS Pharma, Rosenberg, Germany) was selected as model powder based on a raw material database (Van Snick et al., 2018) which included a wide variety of characteristics. No lubrication or pre-treatment of MCC was performed prior to the tabletting experiments.

2.1. Experimental tableting set-up

All experiments were performed on a rotary tablet press (MODUL™ P, GEA Process Engineering, Halle, Belgium). The powder flows from the material hopper by means of a rotary valve (controlled via a level-sensor) in the feed tube to finally enter the feed frame (Fig. 1). The level sensor ensures a constant fill level of the feed tube in order to guarantee a constant overhead pressure on the powder in the feed frame throughout all tableting runs. The turret was mounted with 10 cylindrical flat-faced Euro B punch pairs, while the fill-depth was fixed at 8 mm for all experiments. To perform experiments at different overfill levels of the experimental design, the overfill cams were switched between 8, 10 or 12 mm. For each experiment, the punch positions were adjusted to reach an average pre-compression displacement (PCD), pre-compression force (PCF) and main compression force (MCF) of 0.5 mm, 2 kN and 15 kN, respectively, while no main-compression displacement (MCD) was allowed. The MultiControl 5 software package (GEA Process Engineering, Belgium) controlled the Modul™ P and logged a wide variety of in-line process responses (e.g. PCD, MCF, punch positions) at 1 s intervals. The tablet sampling station was connected to an external balance (K-sampler, Coperion K-tron, Niederlenz, Switzerland), logging the weight gain every second to determine the steady state phase based on the tablet output. All available control loops of the press (i.e. weight, force or displacement control) were deactivated to assure a correct assessment of the die-filling step, which would otherwise be influenced by the compensating control systems.

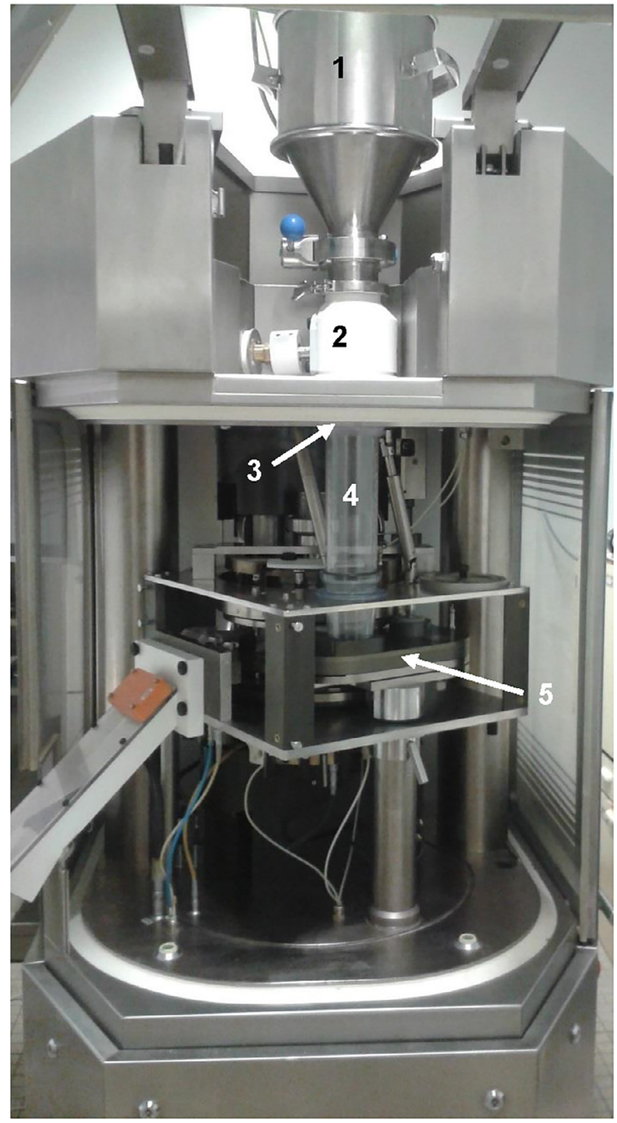

Fig. 1. Experimental set-up of the GEA Modul™ P tablet press: (1) material hopper, (2) rotary valve, (3) level sensor on (4) plexiglass feed tube and (5) feed frame.

2.2. Feed frame design

A conventional two-compartment feed frame was used which consists of a top plate with a sealable deaeration opening, two coplanar paddle wheels and a base plate with a slit where the dies pass (Fig. 2). Powder is delivered into the feed frame by an opening above the first,