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Continuous direct compression as manufacturing platform for sustained release tablets

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ABSTRACT

This study presents a framework for process and product development on a continuous direct compression manufacturing platform. A challenging sustained release formulation with high content of a poorly flowing low density drug was selected. Two HPMC grades were evaluated as matrix former: standard Methocel CR and directly compressible Methocel DC2. The feeding behavior of each formulation component was investigated by deriving feed factor profiles. The maximum feed factor was used to estimate the drive command and depended strongly upon the density of the material. Furthermore, the shape of the feed factor profile allowed definition of a customized refill regime for each material. Inline NIRs was used to estimate the residence time distribution (RTD) in the mixer and monitor blend uniformity. Tablet content and weight variability were determined as additional measures of mixing performance. For Methocel CR, the best axial mixing (i.e. feeder fluctuation dampening) was achieved when an impeller with high number of radial mixing blades operated at low speed. However, the variability in tablet weight and content uniformity deteriorated under this condition. One can therefore conclude that balancing axial mixing with tablet quality is critical for Methocel CR. However, reformulating with the direct compressible Methocel DC2 as matrix former improved tablet quality vastly. Furthermore, both process and product were significantly more robust to changes in process and design variables. This observation underpins the importance of flowability during continuous blending and die-filling. At the compaction stage, blends with Methocel CR showed better tabletability driven by a higher compressibility as the smaller CR particles have a higher bonding area. However, tablets of similar strength were achieved using Methocel DC2 by targeting equal porosity. Compaction pressure impacted tablet properties and dissolution. Hence controlling thickness during continuous manufacturing of sustained release tablets was crucial to ensure reproducible dissolution.

Abbreviations: CI, compressibility index; Cin (t), tracer concentration in the inlet stream; Cout (t), tracer concentration in the outlet stream predicted by macro-mixing model; c(t), concentration profile RTD; d, tablet diameter; e(t), RTD function; e(θ), Normalized RTD function; F, tablet crushing force; FF316, spray dried lactose; ffc, flow function coefficient; ff_p, flow weighed for bulk density; ff_{rho}, flow weighed for density under consolidation; HR, hausner ratio; IAR, immediate axial recovery; k, kinetic constant power law model; MgSt, magnesium stearate; M_t, amount of drug released at time t (power law model); M_∞ amount of drug released after infinite time (power law model); n, release exponent power law model; n_{tanks}, number of continuous stirred tank reactors; NAP, naproxen; NIRs, near infrared spectroscopy; p, plug-flow volume fraction; PLS, Partial Least Square; Pe, Péclet number; R^2, coefficient of determination; RMB, radial mixing blade; rpm, revolutions per minute; RSD, residual standard deviation; RSD_{Cout}, residual standard deviation on Cout of macro-mixing model; RSD_{cu}, residual standard deviation on tablet content; RSD_{wv}, residual standard deviation on tablet weight; RSD_{ss}, steady state blend uniformity, residual standard deviation predicted NAP content; RSD_{if}, short term blend uniformity, residual standard deviation in case of ideal feeding; RTD, residence time distribution; SiO_2, fumed silica; Starch 1500, partially pre-gelatinized starch; $t_{20\%}$, time (h) to reach 20% drug release; $t_{50\%}$, time (h) to reach 50% drug release; T, tablet thickness; t_m, mean residence time; t_{min}, minimum residence time or lag time; V_{screw}, volume dispensed per screw revolution; Q^2, goodness of prediction; ε_{powder}, powder porosity; ε_{tablet}, tablet porosity; ε_{fill}, screw flight fill fraction; ρ_{app}, apparent tablet density; ρ_{bulk}, bulk density; $\rho_{consolidation}$, density under consolidation; ρ_{screw}, density at the screw inlet; ρ_{tapped}, tapped density; ρ_{true}, true density; σ_{tm}^2, variance; σ_ϑ^2, normalized variance; Θ, dimensionless time; ω_{screw}, screw rotation rate.

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1. Introduction

Interest in continuous processing is gaining momentum for pharmaceutical drug product manufacturing. Although drug products are traditionally manufactured via a series of batch-wise unit operations (Engisch and Muzzio, 2015a, 2015b), continuous processing offers several advantages to improve the manufacturing efficiency of solid dosage forms: reduced costs through faster development and less scale-up, smaller equipment footprint and elimination of intermediate storage (Vercruysse et al., 2013). Implementation of in-line process analyzers allows to monitor continuous processes which improves process understanding. This enables the design of a process control and real-time-release strategy which should ultimately improve the quality of the end product (Fonteyne et al., 2015; Simonaho et al., 2016).

Although direct compression is an inherently continuous technique, simple unit operations preceding tableting (i.e. weighing and blending) are historically performed in batches. To enable continuous direct compression, the integration of continuous powder feeding units, a continuous dry powder mixer and tablet press is required. A handful of research papers recently described the feeding unit operation (Cartwright et al., 2013; Engisch and Muzzio, 2014, 2012, 2015b; Meier et al., 2016). Feeders can transfer problems of composition and flow rate variability to subsequent unit operations when their flow rate variability is not well balanced with the amount of axial mixing within the blender. Therefore, the ability to accurately dose a powder over time is a key challenge within the overall manufacturing process. Continuous mixing studies previously focused on the influence of process and design variables on the mixing efficiency and flow behavior within mixers (Pernenkil and Cooney, 2006). Multiple models are available in the literature to describe mixing and transport of particles through a continuous mixer (Fogler, 2006). The main limitation of using residence time distribution (RTD) as a predictive tool for mixing performance (Levenspiel, 1999) is its inability to capture micro-mixing. This is especially important for pharmaceutical blending processes as they combine high product uniformity requirements with small sample sizes. Studies correlating mixing performance with RTD suggested better mixing performance when the RTD is broader (Gao et al., 2011) whilst other studies suggested the performance is governed by the number of revolutions (Vanarase et al., 2010; Portillo et al., 2008). Due to its importance in batch-wise processing, an impressive number of experimental and conceptual compaction studies have been presented (Yu et al., 2014). Patel et al. (2006) underpinned the importance of material properties and tableting speed on compressibility, tabletability and compactibility

This work is an extension of previous studies as experimental and/or conceptual knowledge was applied to each unit operation of an integrated continuous direct compression process. Reports on characterization of integrated from-powder-to-tablet continuous manufacturing platforms remain limited (Ervasti et al., 2015; Järvinen et al., 2013a, 2013b; Simonaho et al., 2016; Vercruysse et al., 2013). Moreover, none of the described systems utilized an automated hopper refill system which is a critical point within the manufacturing process (Engisch and Muzzio, 2015b). Continuous direct compression of an immediate release formulation was first reported by Järvinen et al. (2013a, 2013b). Tablets with good mechanical properties were produced although pharmacopeial uniformity requirements were not met under some conditions. The continuous manufacturing of extended release tablets via continuous direct compression was up to now exclusively investigated by Ervasti et al. (2015). They mainly investigated the impact of particle size (active and HPMC), drug load and mixer speed on product quality. HPMC particle size was a critical material attribute as it impacted the quality attributes of sustained release tablets such as weight variability and tablet strength (Ervasti et al., 2015). Tablet properties were more robust when a better flowing HPMC was incorporated as hydrophilic matrix former although drug release remained prone to mixer settings. Moreover, tablet quality showed significant variability over time as well as within one grab sample. In addition, the mixing performance was not related to the powder flow behavior within the mixer. Furthermore, a low system flow rate was selected (3.5 kg/h) throughout their study. Clearly, significant challenges need to be overcome to enable continuous direct compression of sustained release formulations. Among them, in depth characterization of the continuous mixing stage, improving product quality and exploring the impact of operating at flow rates relevant for pharmaceutical manufacturing.

This paper is organized as follows: the employed continuous direct compression manufacturing platform is introduced in Section 2. The used materials and applied methods are described in Sections 3 and 4, respectively. The obtained results are discussed in Section 5. First, the properties of each material and blend are elucidated (5.1). Secondly, the results of a fundamental loss-in-weight feeder characterization procedure are interpreted (5.2). Thirdly, an experimental design was conducted with Methocel CR grade to understand the impact of impeller configuration and speed on process and product (5.3). Next, the impact of drug load on the mixing performance was verified and related to the blend properties and powder flow within the mixer (5.4). Finally, the impact of HPMC grade and flow rate was assessed (5.5). Conclusions of this work are presented in Section 6.

2. Continuous direct compression equipment

The CDC-50 (GEA APC Pharma Solids, Wommelgem, Belgium) combines material handling, loss-in-weight feeding, two stage continuous blending, compression and in-line NIRs to monitor blend uniformity in an integrated manufacturing system (Fig. 1).

The individual materials are transferred to dedicated top up systems through vacuum conveying or gravity. The vacuum top up system consists of a conical hopper (3.2 L) with level sensor to regulate pneumatic powder supply. The gravity feed system consists of a cylindrical feed tube and is used when powders undergo triboelectric charging during vacuum transfer. Both systems are connected to a rotating top-up valve (0.4, 0.8, 1.2 or

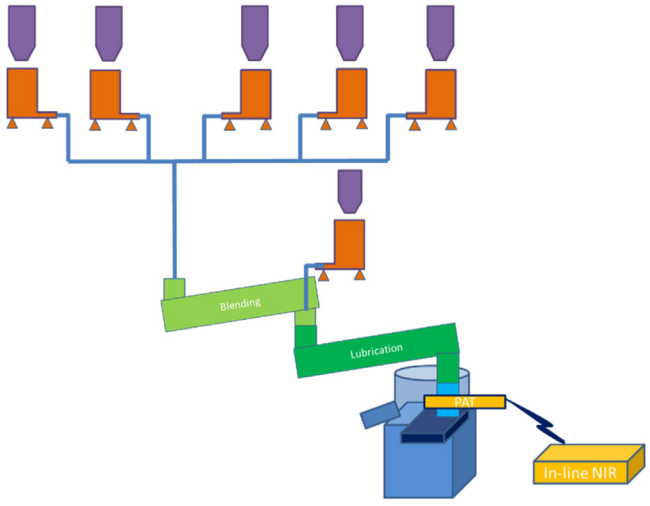

Fig. 1. Flowsheet of CDC-50. Powder supply and refill mechanism (■), twin screw feeding (■), blending (■), lubrication (■), feed tube (■), in-line NIRs as PAT tool (■) and tablet press (■).