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Provoking an end-to-end continuous direct compression line with raw materials prone to segregation

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ABSTRACT

Continuous manufacturing of solid oral dosage forms is promising for increasing the efficiency and quality of pharmaceutical production and products. In this study a whole train continuous direct compression (CDC) line has been provoked using challenging formulations typically prone to segregation in batch powder processing. Industrial compositions including components with variable size, bulk density and cohesive nature were selected. An experimental design, including variables such as API/mannitol particle size, API amount, powder feed rate and mixer speed, enabled the output quality of the provoked process to be assessed. Contrary to previous studies, a broader range of finished tablet quality attributes were probed, including content, uniformity of content, tensile strength as well as release performance. Overall, the continuous direct compression line was found to be a capable and efficient manufacturing process for the challenging compositions studied and surprisingly tolerable to handle the materials susceptible to segregation in typical batch settings. As expected, and given the 'fixed' apparatus configuration used in this study, the particulate material properties were found to have the most significant impact on the finished tablet quality attributes. The results emphasize the importance for taking a holistic approach when developing the operational windows and the strategy for control, e.g. by integrating the appropriate material properties, the actual apparatus design, and the relevant formulation design. The CDC line's ability to handle cohesive materials also seem to be one of the key advantages, thus confirming the recent promising results from other continuous direct compression studies.

1. Introduction

While the pharmaceutical industry is well known to be innovative with regards to developing new drug products, its manufacturing efficiency have lagged behind when compared to many other industries. Traditionally, most manufacturing operations have been carried out in batch mode, regardless of advantages related to continuous processing. Fortunately, changing the production from batch to continuous mode has become increasingly more appealing to the industry as well as accepted by regulatory authorities (Boukouvala et al., 2012; Vervaet and Remon, 2005; Schaber et al., 2011; Yin and Clayton, 2014; Lee et al., 2015).

When using continuous mixing followed by direct compression, several unit operations (granulating, drying, particle sizing) can be avoided which will speed up and simplify the process compared to batch granulation methods. Other advantages of continuous mixing compared to batch processing are smaller mixer size, less material in the process at each time instance and consistent mixing performance since the mixer is operating at steady-state most of the time. In addition, discharge issues such as ratholing and segregation commonly observed with batch processing can be avoided, and in the ideal case no sampling would be needed during the process (Alexander et al., 2001; Berthiaux et al., 2008).

One major challenge during processing of particulate solids is risk for segregation. In systems of free flowing non-identical solid particles segregation may easily occur (Lacey, 1954; Bridgwater, 1976; Staniforth, 1985; Fan et al., 1990; Poux et al., 1991; Alexander et al., 2001; Oka et al., 2017). Many factors may influence the segregation tendency. The primary factor is the particle size difference among the components of the mixture (Prescott and Hossfeld, 1994; Duffy and Puri, 2002; Tang and Puri, 2007; Oka et al., 2017). Secondary factors are particle shape, density and surface texture (Yang, 2006; Tang and

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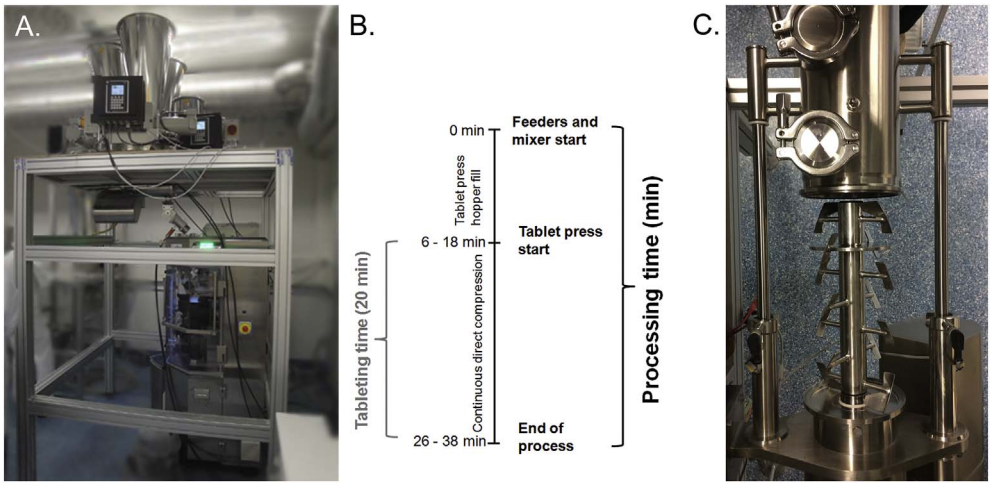

Fig. 1. A. The continuous direct compression manufacturing set-up used in the experiments. B. A timeline describing the process phases. C. Photo of the blender used.

Puri, 2007; Oka et al., 2017). In addition, it is important to consider that each raw material have an inherent natural variability on the particle level that can translate into material variability also on the powder bulk level. Consequently in a final formulated powder blend, all these factors must be weighted in when evaluating the risk for segregation and the potential risk to negatively impact the finished tablet quality. Here, the finished tablet quality may be assessed through multiple tablet quality attributes such as for example; tablet weight, drug content, compactibility and/or dissolution (Sommier et al., 2011). Segregation can also result due to agglomeration of cohesive particles (Remy, 2010). Equally important as the material properties in influencing segregation tendency, is also the design of the equipment and overall process for handling the particulate material throughout the series of unit operations utilized (Tang and Puri, 2004; He et al., 2013). For instance, the height of any eventual free falls in the manufacturing line needs to be minimized. Thus, maybe the most important phase in a direct compression process in terms of segregation is the discharge of the mixer (Staniforth, 1985; Liss et al., 2004; Conway et al., 2005). For low drug load compositions the consequences of segregation on powder processing performance becomes particularly challenging especially during direct compression manufacturing (He et al., 2013).

Many reports on continuous manufacturing have been focused on mixer set-up, design, and operational process parameters (Portillo et al., 2008; Gao et al., 2011; Vanarase and Muzzio, 2011). Also the effect of some raw material properties on mixing behavior has been published (Porion et al., 2004; Berthiaux et al., 2008; Vanarase and Muzzio, 2011; Boukouvala et al., 2012; Van Snick et al., 2017a; Van Snick et al., 2017b). However, there are so far only a few studies on the interaction of multiple material properties and process parameters in integrated whole train continuous mixing and direct compression process systems (Järvinen et al., 2013a, 2013b; Engisch and Muzzio, 2015; Ervasti et al., 2015; Lakio et al., 2016; Pawar et al., 2016; Van Snick et al., 2017a, 2017b) The authors of the present work have previously concluded that material properties have a great effect on the properties of tablets manufactured in a whole train continuous mixing and direct compression line (Ervasti et al., 2015; Lakio et al., 2016). Notably, these recent results indicate that the integrated continuous mixing and direct compression could efficiently handle very challenging material compositions and consistently deliver intended output quality even for advanced tablet functionalities such as extended release performance (Ervasti et al., 2015; Lakio et al., 2016; Van Snick et al., 2017a). However, there is still an insufficient understanding how far a fully integrated continuous mixing and direct compression line can be stressed before it fails to deliver high quality finished tablets consistently.

The aim of this study was to provoke a whole train continuous direct compression line, including integrated mixing and direct compression (denoted the CDC line) with challenging formulations. The formulations and associated materials studied here were selected from those prone to exhibit segregation tendency in typical batch process settings, for example due to large particle size differences and wide range of bulk densities. The CDC line output performance was assessed in terms of the impact of several formulation and material parameters on multiple finished tablet quality attributes. Moreover, the CDC line was mainly operated in this study as a 'fixed' apparatus configuration, albeit a few process parameters were also challenged such as for example the powder feeders that were forced to the very low-end of their operational range, which could potentially cause feeding problems. By using powders with disparate raw material properties together with challenging process settings the previous indication of high efficiency of the CDC line was further evaluated regarding susceptibility to segregation.

Based on pre-tests, the experimental design was spanned out to ensure inclusion of provoking conditions that would constitute boundary operational settings, in particular for a 'fixed' apparatus configuration. The experiments were structured to mimic four different CDC line tablet manufacturing scenarios:

- Base scenario: Robust processing and intended tablet quality (Base Scenario)
- Three provocation scenarios:
  - low API load composition - segregation risk (Scenario 1)
  - coarser API material - segregation risk (Scenario 2)
  - coarser API and filler material - segregation and poor compactibility risk (Scenario 3)

For further details, see Materials and methods section and the overview Fig. 10.

2. Materials and methods

2.1. Continuous manufacturing line

The integrated continuous direct compression (CDC) line used in this study consists of feeders, a blender, and a tablet press. The feeders and the mixer were adjusted and controlled by an in-house software, and the risk of segregation was minimized as no conveyors were used. The CDC line is depicted in Fig. 1 and has been described in detail in previous reports, and therefore summarized in brief in the subsections below.

2.1.1. Feeders

The following feeders were used in the experiment: K-ML-D5-KT20,