International Journal of Pharmaceutics 495 (2015) 290–301

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Continuous manufacturing of extended release tablets via powder mixing and direct compression

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ARTICLE INFO

Article history:
Received 9 June 2015
Received in revised form 23 August 2015
Accepted 24 August 2015
Available online 28 August 2015

Keywords:
Continuous manufacturing
Direct compression
Continuous mixing
Extended release
HPMC
Adaptive control

ABSTRACT

The aim of the current work was to explore continuous dry powder mixing and direct compression for manufacturing of extended release (ER) matrix tablets. The study was span out with a challenging formulation design comprising ibuprofen compositions with varying particle size and a relatively low amount of the matrix former hydroxypropyl methylcellulose (HPMC). Standard grade HPMC (CR) was compared to a recently developed direct compressible grade (DC2). The work demonstrate that ER tablets with desired quality attributes could be manufactured via integrated continuous mixing and direct compression. The most robust tablet quality (weight, assay, tensile strength) was obtained using high mixer speed and large particle size ibuprofen and HPMC DC2 due to good powder flow. At low mixer speed it was more difficult to achieve high quality low dose tablets. Notably, with HPMC DC2 the processing conditions had a significant effect on drug release. Longer processing time and/or faster mixer speed was needed to achieve robust release with compositions containing DC2 compared with those containing CR. This work confirms the importance of balancing process parameters and material properties to find consistent product quality. Also, adaptive control is proven a pivotal means for control of continuous manufacturing systems.

1. Introduction

In a vast majority of modern industries continuous manufacturing has over the years gradually replaced traditional step-by-step manufacturing of products. The start-to-finish production lines generally provides improved efficiencies. In the pharmaceutical industry on the other hand, where highly advanced medicinal products are produced, adoption of new manufacturing technologies is rather slow and batch processing continues to be the dominating process platform. Several reasons have been adressed that underpins this slow manufacturing evolution such as regulatory policies, poor intellectual property incentives and lack of proven off-the-shelf equipment (Plumb, 2005; Nicholson, 2014; Lee et al., 2015). During recent years industry and academia leaders have taken significant initiatives to progress continuous manufacturing (Mascia et al., 2013; International Symposium on Continuous Manufacturing of Pharmaceuticals, White Papers, 2014; Poechlauer et al., 2012; Buchholz, 2010). In addition, the regulatory and quality considerations have recently been summarized and assessed emphasizing general support from health agencies for implementation of continuous manufacturing (Lee et al., 2015; Allison et al., 2015; ICHQ8-Q11 guidances). Nevertheless, remaining gaps and challenges are identified that must be adressed to facilitate wider adoption and implementation of continuous manufacturing as a viable approach in pharmaceutical industry.

For marketed drug products the most common dosage form is a tablet. In tablet manufacturing, typical disadvantages of batch processing are associated with scale-up, lack or insufficient real time quality control, insufficient process understanding, and long manufacturing cycles (Leuenberger, 2001a,b; Vervaet and Remon, 2005). Here, continuous manufacturing holds a great potential to overcome some or all of these classical problems. For example, scale-up of production volumes is achieved with the same equipment through longer processing times rather than by scaling process equipment geometries as with batch processing (Leuenberger, 2001a). Thereby, manufacturing facilities can be made more compact and costs for heating/cooling, ventilation and other

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http://dx.doi.org/10.1016/j.ijpharm.2015.08.077
0378-5173/

costs can be reduced (Plumb, 2005; McKenzie et al., 2006; Spencer et al., 2011). Finally, to enable appropriate control of continuous manufacturing lines advanced on-line and in-line process and material sensors will be a prerequisite and offer opportunities to improved process understanding, product quality and yield increase. In all, these advantages have raised a large interest in the pharmaceutical industry for continuous manufacturing, albeit, extensive experience with pharmaceutical applications is still lacking.

The most straightforward example of a continuous tablet manufacturing line is the integration of continuous dry powder mixing and continuous direct compression. Here continuous powder feeders have an essential role for the overall performance of the continuous tablet manufacturing line. For example the tablet quality will fluctuate if there is a large variability in the inflow composition, even if the mixer and tablet press would perform perfectly. Hence it is crucial to ensure that the feed rate of each bulk material is controlled accurately (Marikh et al., 2005; Pernenkil and Cooney, 2006; Portillo et al., 2008). Loss-in-weight (LIW) feeders have been shown to be the most accurate material feeding devices for dry powder based continuous pharmaceutical manufacturing lines. Most of the research considering LIW feeders has concentrated on the effect of powder properties and the feeder design on the performance (Engisch and Muzzio, 2012). The effect of screw design, charging container configuration, and interparticle cohesion on solid flow has been studied by Hou et al. (2014). They identified formation of three flow regimes in a complicated manner in a screw feeder that must be considered to achieve optimized operation.

Continuous mixing is currently a widely studied area (Pernenkil and Cooney, 2006; Berthiaux et al., 2008; Portillo et al., 2008, 2009, 2010). Mechanistic insight into optimization of continuous dry powder mixing has been reported by Gao et al. (2011) who demonstrated improved performance by increasing blade speed of a mixer while keeping a constant axial velocity. Portillo et al. (2008) studied a continuous dry powder mixer, where the impeller rotation, the operation angle, the number of blades and the angle of blades could be adjusted. They found that decreasing the impeller rotation rate and increasing the upward angle of the mixer gave optimal processing conditions for that particular mixer. The mean residence time, the time that the powder is inside the mixer, has been one of the main variables affecting the mixing performance (Portillo et al., 2008, 2009, 2010; Vanarase and Muzzio, 2011). When the optimal mixer speed is studied, mixer properties, material properties and total mass flow material have to be considered. While engineering aspects of continuous dry powder mixing in general have been extensively studied, also beyond pharmaceutical powders (Pernenkil and Cooney, 2006; Berthiaux et al., 2008; Portillo et al., 2008, 2009, 2010; Bridgewater, 2012), systematic studies comprising material parameters are so far fewer. In addition, studies on the performance and operational optimization of complete continuous tablet manufacturing trains are also few. Vanarase and Muzzio (2011) reported that mixing performance was largely dominated by the material properties of the mixture, while in a later article they found that the bulk density was the key material parameter affecting the mean residence time (Vanarase et al., 2013). The importance of incorporating powder material properties when assessing system performance was also concluded by Boukouvala et al. (2012) in a recent flowsheet modeling and sensitivity analysis of a whole continuous tablet manufacturing line.

Previous studies considering continuous manufacturing of tablets have focused on probing uniformity of product performance only with regards to drug substance assay, drug distribution and mechanical properties of tablets. In the present work the viability of integrated continuous mixing and compaction processes for manufacturing of extended-release matrix tablets is investigated. The performance of tablets based on this formulation principle relies not only on assuring assay and proper distribution of the drug substance but also on the ability to provide extended and robust drug release *in-vivo*. The latter depends mainly on the polymeric matrix and its distribution in the composition which also needs to be considered during continuous powder processing. Commercially available hydroxypropyl methyl cellulose (HPMC) grades are mostly designed for wet granulation and have a relatively narrow particle size with a low mean particle size and therefore poor powder flow characteristics. Those grades are therefore not suitable for high-speed direct manufacturing processes. However, direct compressible grades of HPMC has recently been launched and their performance have been investigated (Mohamed et al., 2013; Rogers et al., 2013; Heiman et al., 2015). Some investigations on direct compression of hydrophilic matrices have been reported previously, but to the best of our knowledge, an integrated continuous manufacturing via continuous dry powder mixing and continuous direct compression has not yet been demonstrated. The overall aim of the current work was to explore continuous mixing and direct compression with a challenging formulation design with regards to powder characteristics and composition. The design included low dose compositions for which drug substance uniformity aspects were tough and a relatively low amount of the matrix former (HPMC) for which proper distribution was essential. Standard CR as well as DC grade HPMC were included in the study. The processing settings were varied broadly to stress the system further with the aim to understand the critical relationship between raw materials and final product performance (tablet mass variability, tablet tensile strength, drug assay and drug release). The intent was both to enable a deeper understanding of the critical relationship between raw materials and final product performance but also to initially explore how the feeder and compression data relate to final quality.

2. Materials and methods

2.1. Materials

Two different grades of hydroxypropyl methylcellulose (HPMC) were used as matrix formers: standard wet granulation grade, Methocel K100 Premium LV CR (CR, Dow Chemical Company, Midland, Michigan, USA) and a new direct compressible grade, Methocel K100 Premium LV DC2 (DC2, Dow Europe GmbH, Bomlitz, Germany). The model active substance was ibuprofen (Zhengzhou Debao Fine Chemical Co. Ltd., Henan, China). Two different ibuprofen particles sizes (IbuPS) were used: (1) as received from the supplier (large IbuPS) and (2) small IbuPS prepared by ball milling (Retch S1, Haan, Germany). Mannitol (Parteck M200, Merck KGaA, Darmstadt, Germany) was added as a soluble filler and sodium stearyl fumarate (PRUV, Moehs, Barcelona, Spain) as a lubricant.

2.2. Design of experiment

The study was performed as an experimental design with four factors: HPMC particle size (HPMC PS), ibuprofen particle size (IbuPS), ibuprofen load (Ibu%) and mixer speed. The design was a full factorial with 19 runs. However, poor flow of the powder blends were observed when low IbuPS and high Ibu% were combined and the associated manufacturing difficulties led to the exclusion of the factor combination. Thus a d-optimal design was adopted; the process parameters are listed in Table 1. MODDE 10 (Umetrics MKS AB, Umeå, Sweden) was used both to construct the experimental design and for evaluation of data. All models were fitted with multiple linear regression (MLR).

For the center point of the design (N17, N18 and N19), a 1:1 mixture of the two HPMC grades was prepared. In addition, a