International Journal of Pharmaceutics 511 (2016) 659–668

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Achieving a robust drug release from extended release tablets using an integrated continuous mixing and direct compression line

Satu Lakio[a,*], Pirjo Tajarobi[a], Håkan Wikström[a], Magnus Fransson[a], Johan Arnehed[a], Tuomas Ervasti[b], Simo-Pekka Simonaho[b], Jarkko Ketolainen[b], Staffan Folestad[a], Susanna Abrahmsén-Alami[a]

[a] AstraZeneca Gothenburg, Pepparedsleden 1, SE-43183 Mölndal, Sweden
[b] School of Pharmacy, Yliopistonranta 1, University of Eastern Finland, FI-70211, Finland

ARTICLE INFO

Article history:
Received 14 June 2016
Received in revised form 20 July 2016
Accepted 23 July 2016
Available online 26 July 2016

Keywords:
Continuous direct compression
Continuous mixing
Dissolution
Extended release
Hydroxypropyl methylcellulose
Percolation
Robust drug release

ABSTRACT

In the present work the viability of integrated continuous mixing and compression processes for manufacturing of extended release (ER) matrix tablets was investigated in terms of dissolution behavior. The purpose was also to evaluate the combined effect of processing variables and compositional variables on the release robustness. The continuous process was provoked by a challenging formulation design, including variable powder characteristics and compositions of high and low amount of poorly soluble and poorly flowing drug substance (ibuprofen). Additionally a relatively low amount of two different ER matrix former grades (standard granulation grade CR and direct compression grade DC2 of hydroxypropyl methylcellulose, HPMC) was used to challenge the system. Robust ibuprofen release was obtained faster when HPMC CR was used. However, robust release was also achieved when using HPMC DC2 at high ibuprofen content, even though it took slightly longer time to reach the steady state of the process. Due to its poor flow properties, HPMC CR would be very challenging to use in traditional direct compression. The results showed that by using continuous processing it is possible to manufacture and achieve robust performance of compositions that would not be possible with traditional batch processing due to for instance poorly flowability.

1. Introduction

The benefits of continuous pharmaceutical manufacturing of oral solid dosage forms (OSD) have been discussed a lot in the literature (Vervaet and Remon, 2005; Schaber et al., 2011; Yin and Clayton, 2014). Some of these advantages include lower processing costs, significant time savings, no need for traditional scale-up, more compact manufacturing facilities, as well as more flexible output capacity. When considering continuous mixing and direct compression some additional advantages can be also stated, namely better control over the mixing process, no discharge issues such as ratholing and no need for sampling to determine the end point. In pharmaceutical industry, adaption of new manufacturing technologies has generally been rather slow. There are many reasons for this slow manufacturing evolution such as poor intellectual property incentives, regulatory policies, lack of proven off-the-shelf equipment, and so on. For further background, see the discussions by Plumb (2005), Nicholson (2014), Lee et al. (2015), and references therein. The slow adaptation of new technologies is therefore reflected in that batchwise processes still remain as the dominating platform for OSD drug product manufacture.

Manufacturing of extended release matrix tablets can be a challenging task in both batch and continuous processing and goes beyond manufacturing of immediate release (IR) OSD. 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.

For hydrophilic extended release tablets based on hydroxylpropyl methylcellulose (HPMC) continuous direct compression may provide additional opportunities but is also associated with some challenges. Historically wet granulation has been the most common manufacturing method for HPMC based formulations, but when using water as granulation liquid there is a challenge due

* Corresponding author.
E-mail address: satu.lakio@astrazeneca.com (S. Lakio).

http://dx.doi.org/10.1016/j.ijpharm.2016.07.052
0378-5173/

to hard lump formation and associated poor compaction performance. Instead direct compression may be used to avoid the issues with water granulation. However, commercially available HPMC grades are mostly designed for wet granulation and are normally not suitable for traditional "batch" mixing followed by direct compression due to a small particle size and therefore poor powder flow characteristics. However, directly compressible grades of HPMC have recently become available and their performance has been investigated in several papers (Mohamed et al., 2013; Rogers et al., 2013; Heiman et al., 2014). In spite of some investigations on direct compression of hydrophilic matrices being reported previously, to the best of our knowledge, integrated continuous manufacturing using continuous dry powder mixing and continuous direct compression has only be published in our previous paper (Ervasti et al., 2015). In that study, we demonstrated that extended release matrix tablets can be successfully manufactured using an integrated continuous mixing and direct compression manufacturing line. In fact dissolution behavior of tablets manufactured using continuous direct compression in general has not been studied extensively before. Järvinen et al. (2013) measured paracetamol release after continuous direct compression but their formulation contained only MCC and paracetamol and thus the release was found to be driven by the compression force rather than disintegrant activity in the formulation. Thus API was released via disintegration rather than dissolution.

In the present work, the viability of integrated continuous mixing and compression processes for manufacturing of extended release matrix tablets was investigated mainly in terms of dissolution behavior. The continuous process was challenged by a formulation design, including variable powder characteristics and compositions of high and low amount of the drug substance (ibuprofen). Additionally a relatively low amount (32%, w/w) of the extended release matrix former (HPMC) was used in order to maximize the amount of filler (mannitol) for better compaction and powder flow. At these low amounts of matrix former there is a known risk that formulations may show poor release robustness (Tajarobi et al., 2009). This has been shown to be even more challenging when using the larger particle sized HPMC matrix formers developed to be more suitable for direct compression (Heiman et al., 2014). Thereby the opportunity to evaluate the process using several different performance aspects was enabled. In addition, the design of present work gave the opportunity to evaluate the combined effect of continuous processing variables and compositional variables on the release robustness.

2. Materials and methods

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). For the centre points 50:50% (w/w) blend of CR and DC2 was manufactured. The model drug 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.

2.1. 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 (Table 1). However, low IbuPS and high Ibu% combination was excluded due to extremely poor flow. Modde 10 (Umetrics MKS AB, Umeå, Sweden) was used both to construct the experimental design and for evaluation of the dissolution data. The model was fitted with multiple linear regression (MLR).

In all experiments, the concentrations of HPMC and PRUV were constant (32% and 2% w/w, respectively), the ibuprofen concentration was changed within three levels (2%, 15% or 22% w/w) as well as the concentration of mannitol (44%, 51% or 64%, w/w). The total feed rate of powders was kept constant at 3.5 kg/h.

2.2. Process description

The continuous mixing and direct compression manufacturing set-up used in the study is described in Fig. 1A. The feeding, mixing, and compressing parts are all integrated into a complete continuous tablet manufacturing line. Three kinds of LIW feeders (K-Tron, Types K-ML-D5-KT20 and K-CL-SFS-KT20 (two different versions), Niederlenz, Switzerland) were used in the study. K-ML-D5-KT20 fed HPMC and mannitol an also ibuprofen with high content (15–22%) and K-CL-SFS-KT20 fed PRUV and ibuprofen with low content (2%). Raw materials were fed from the feeders directly into the continuous mixer (Modulomix, Hosokawa Micron, Doetinchem, the Netherlands). After mixing, the powder mixture was guided (flow controlled by gravity) into the hopper of the tablet press (PTK-PR1000, PTK CO., Ltd, Incheon, Republic of Korea). This very simple set-up enabled conducting experiments without any conveyors, thus reducing the risk of segregation due to transport. The feeders and the mixer were adjusted and controlled by an in-house software, and data from the feeders were acquired for later analysis. The tablets were compacted with a turret speed of 48 rpm using eight 7 mm concave punches to produce tablets with a target weight of 150 mg. Compression force between 5 and 9 kN was used in this study. The detailed description about the continuous line (including feeders) and used parameters can be found in Ervasti et al. (2015).

The timeline of the process is described in Fig. 1B. To start processing, the feeders and the mixer were first turned on (time point 0) and the powder mixture was collected into the hopper of the tablet press for 12 min to serve adequate fill level for the press.

Table 1
D-optimal experimental design worksheet.

Run	Speed (rpm)	HPMC PS (μm)	Ibu PS (μm)	Ibu (%)
N1	300	77	30	2
N2	1200	77	30	2
N3	300	120	30	2
N4	1200	120	30	2
N5	300	77	66	2
N6	1200	77	66	2
N7	300	120	66	2
N8	1200	120	66	2
N9	300	77	66	22
N10	1200	77	66	22
N11	300	120	66	22
N12	1200	120	66	22
N13	300	77	30	15
N14	1200	77	49	22
N15	300	120	49	22
N16	1200	120	30	15
N17	750	100[a]	49	15
N18	750	100[a]	49	15
N19	750	100[a]	49	15

[a] A 50:50% (w/w) mixture of HPMC CR and DC2 was used in center points.