Powder Technology 331 (2018) 236–243

Contents lists available at ScienceDirect

Powder Technology

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

Control of a system of loss-in-weight feeders for drug product continuous manufacturing

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ARTICLE INFO

Article history:
Received 31 October 2017
Received in revised form 26 February 2018
Accepted 12 March 2018
Available online 17 March 2018

Keywords:
Loss-in-weight feeders
Ratio control
Continuous manufacturing

ABSTRACT

Loss-in-weight (LIW) feeders are used to dispense individual materials to the downstream unit operations in continuous drug product manufacturing processes. The purpose of this work was to identify potential material feeding failure modes and demonstrate how a ratio control loop can be used to improve performance for a system of feeders when these disturbances occur and at steady operation. Three feeding failure modes were identified and studied in detail. First, excessive mass flow variability about the setpoint was examined. Next, inaccurate feeding (e.g. consistent over- or under-feeding) relative to setpoint was investigated. Finally, special-cause transient disturbances were explored, which are often generated by hopper refills, external influences to the scale, and/or changes in material properties and flow. These feeding issues impact both the precision and accuracy of the feeding operation. Experiments were executed on a continuous direct compression process utilizing two control modes for the feeders, local (individual feeder control) and ratio (system control in addition to individual feeder control) modes. Ratio mode was proven to be more effective than local mode for feeding the unit formula to the downstream process. Both the precision and accuracy of the output from the system of feeders were improved when using ratio control. For formulas with high feeding variability for drug substances (DS) and excipients, using ratio control improved the DS concentration %RSD at the outlet of the feeders from 5.1% to 2.1% and excipient concentration %RSDs ranging from 2.3–4.9% to 2.3–2.7%. For formulas with good dispensing precision but poor accuracy, ratio control was used to demonstrate improved DS Feeding Accuracy from 97.3% to 101.0% of target. Finally, for formulas that encounter transient disturbances while running in the continuous process, ratio control mode was shown to improve both accuracy and precision during the disturbances, improving the DS concentration %RSDs from 1.9–3.7% to 0.7–1.3% and accuracy values from 104.0–106.5% to 100.2–102.0% of target. Ratio control complements proper equipment configuration selection and individual feeder controller optimization as appropriate techniques used to implement a well performing system of feeders.

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1. Introduction

The use of continuous processes for drug product manufacturing in the pharmaceutical industry is expanding due to many potential benefits. As a part of the continuous manufacturing process, a system of loss-in-weight (LIW) feeders is used as an upstream unit operation to dispense the materials in the unit formula to the downstream process. Individual feeders house different materials and continuously feed these materials at the appropriate mass flow rate ratios according to the formulation. As the inputs to a continuous process greatly affect the output [1], it is critical to have a good understanding of the process inputs and their variability. The FDA states that two of the elements of a well understood process are identifying and explaining all critical sources of variability and using the process to manage that variability [2]. Therefore, the control of the feeding operation is often a primary element of the system control strategy, used to ensure drug product critical quality attributes (CQAs) are achieved.

There are typically two modes of operation for feeders, volumetric and gravimetric. Volumetric mode entails the feeder operating at a constant screw speed, thus theoretically delivering a constant volume of material per unit time. There is no feedback control and thus delivery of a consistent mass flow is reliant on constant material density. Gravimetric mode however utilizes a volumetric feeder mounted on top of a load cell which measures changes in weight over time. A controller is used to adjust the speed of the feeder screws to minimize the error between the measured mass flow and the user-defined setpoint [3]. Robust feed rate control can often be a challenge in pharmaceutical processes due to material flow difficulties and low flow rate requirements, both of which tend to increase feeding variability [4]. LIW feeders are typically preferred over volumetric feeders for applications that require a great deal of precision and accuracy like pharmaceuticals, as by operating gravimetrically, accurate and stable material mass flow can be achieved [3]. As described, LIW feeders utilize controllers in gravimetric mode to

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https://doi.org/10.1016/j.powtec.2018.03.027
0032-5910/© 2018 Published by Elsevier B.V.

Table 1
Theoretical unit Formulas A, B, and C.

Material	Formula A		Formula B		Formula C	
	Material	Conc. %/tablet	Material	Conc. %/tablet	Material	Conc. %/tablet
Drug substance	Croscarmellose sodium	26.3	Micronized acetaminophen	28.8	Croscarmellose sodium	7.6
Excipient 1	Magnesium stearate vegetable	5.3	Magnesium stearate vegetable	3.7	Magnesium stearate vegetable	0.9
Excipient 2	Croscarmellose sodium	42.1	Microcrystalline cellulose 102	56.1	Microcrystalline cellulose 302	88.8
Excipient 3	Croscarmellose sodium	26.3	Croscarmellose sodium	11.3	Croscarmellose sodium	2.7

constantly adjust to weighing errors; however some level of dispensed mass flow variability is still expected. Additionally, maintaining constant mass flow over short periods of time can be challenging as special cause disturbances occasionally occur. For example, disturbances can be caused by material refills, equipment setup issues, changes in material and flow properties, and perturbations from external influences such as vibration or air pressure [5]. These issues can lead to feed rate inaccuracy and material concentration variability. Typical continuous processes contain downstream mixing elements designed to reduce the variability and dampen disturbances from the feeding operation. However, several literature works have found that these disturbances can still propagate downstream and affect both the performance of downstream equipment and product quality [6–9]. For example, Berthiaux et al. demonstrated how feeder refills can affect the quality of the mixture exiting a downstream continuous blender [9]. Therefore, limiting the variability at its source is desired and can lead to enhanced process performance, improved product quality and yield, and reduced dependence on back mixing downstream.

To date, research on enhancing the control and performance of feeders has been primarily focused on two areas: equipment configuration selection and individual feeder controller optimization. Previous works have detailed the process of choosing the appropriate LIW feeder equipment configuration to predict and minimize output variability (feeder size, screw type, agitator, hopper, etc.) according to material properties and desired process parameters. Engisch and Muzzio developed a method for the characterization of LIW feeders such that the proper tooling (screws and screens) were selected depending on the desired feed rate [10]. Wang et al. discussed how material flow properties influence feeding performance and further emphasized the importance of tooling selection [11]. Blackshields and Crean similarly detailed which screw type to use based on powder flow properties [5]. In addition to feeder tooling, multiple hopper designs have been investigated by Cartwright et al. to optimize feeding control of a poorly flowing active pharmaceutical ingredient to a granulation system [12]. Various refill strategies and equipment sets exist to mitigate resulting disturbances. For example, Engisch and Muzzio discussed feed rate deviations caused by hopper refills and suggested a method to gently replenish the hopper rather than high rate refill systems to reduce the propagated disturbance [13]. However, even with optimized hardware, special cause disturbances still occur which can impact the downstream process and product.

In addition to optimizing equipment configuration, selecting the right type of controller and associated parameters are also important for optimal feeding performance. Previous works have evaluated and discussed individual feeder control techniques, primarily focusing on using closed-loop proportional plus integral (PI) or proportional plus integral plus derivative (PID) controllers. For example, Thayalan and Landers provides a complete dynamic model of a gravity-fed powder feeder system including a closed-loop PI controller [14]. Singh et al. investigated control at the system level and implemented a plant-wide control strategy utilizing feedback and cascade control loops including a feeder ratio controller on both roller compaction and direct compression processes [15–17]. These works further demonstrated that closed-loop control compared to open-loop has the potential for improving pharmaceutical manufacturing operations and enhancing product CQAs. However, even after properly configuring the LIW feeder for the material it will feed and optimizing its individual control, some mass flow variability is expected from individual feeders leading to variability in material concentrations dispensed to the downstream system. Therefore, a system based feeder control method of ratio control can be used to further reduce material concentration variability both during steady operation as well as during process upsets. Ratio control is an already well-established control method for manufacturing products in the food and plastics industries. It is commonly used to control material dispensing into downstream unit operations such as continuous mixers and extruders for the production of products such as infant formulas, flour grades, trail mix blends, and plastic resins for example [18]. This beneficial control concept can now be applied in the pharmaceutical industry as continuous processing for drug products has become increasingly prevalent.

This paper details the method of implementing feeder ratio control on a system of feeders and provides data demonstrating its ability to

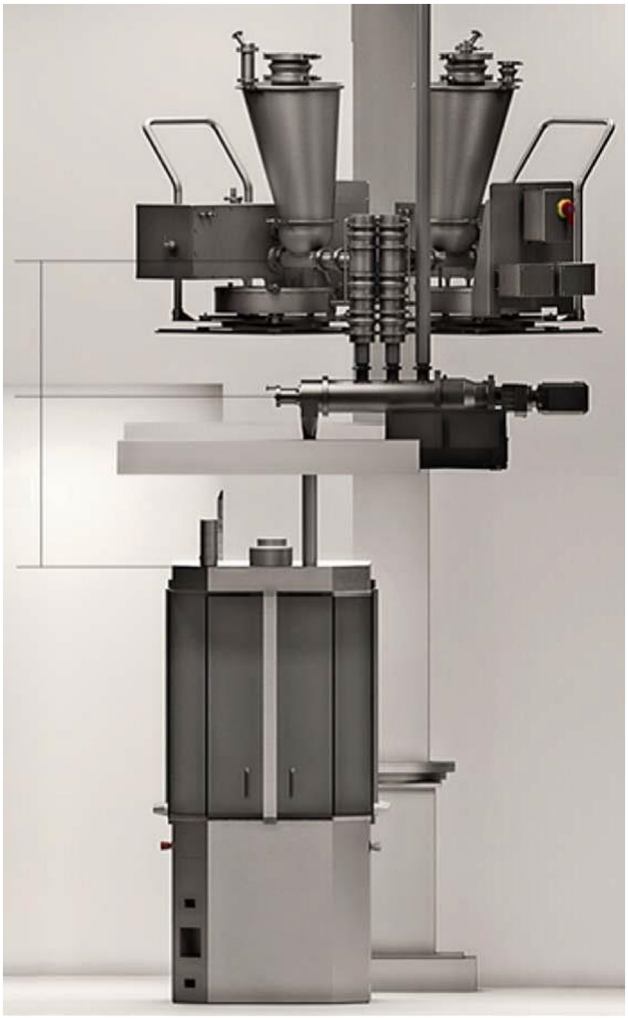

Fig. 1. Lilly's continuous, direct compression manufacturing platform.

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