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Research Paper

Development and implementation of an advanced model predictive control system into continuous pharmaceutical tablet compaction process

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ABSTRACT

In the context of continuous pharmaceutical oral dosage manufacturing, a control system is essential to ensure that the critical quality attributes (CQAs) are maintained within the regulatory constraints by mitigating variations generated in upstream operations. Such a system is essential to the Quality by Design (QbD) paradigm shift, which can ensure that predefined end quality attributes are achieved within an optimal economic and time bracket. In this work, an advanced model predictive control (MPC) architecture integrated with a novel real-time tablet weight measurement method has been development and implemented into a continuous direct compaction tablet manufacturing pilot-plant. The proposed control architecture has the potential to control tablet weight and tablet breaking force simultaneously by systematically decoupling and cascading the control loops. The model predictive control algorithm was experimentally found to be superior to the PID (proportional, integral and derivative) controller and thus, can be utilized for a wide range of applications to improve the quality of pharmaceutical products in continuous manufacturing. The MPC was used to control main compression force and pre compression force using main compression height and fill depth respectively as the actuators. The introduction of this methodology leads to new ways of developing MPC models, tablet weight measurement methods and control strategies that enhance the manufacturability and quality of pharmaceutical tablets.

1. Introduction, background and objectives

Real-time inline/online process monitoring and closed loop feedback/feedforward control systems for a pharmaceutical plant can establish an environment that is capable of achieving Quality by Design (QbD) and Quality by Control (QbC) as opposed to Quality by Testing (QbT) based manufacturing. This approach improves efficiency by making optimal use of time, space and resources while simultaneously satisfying the steep regulatory expectations, flexible market demands, operational complexities and economic limitations. Model predictive control (MPC), which is a closed loop optimization based method, is an effective and proven strategy that has been widely used in process industries such as oil refining, bulk chemical production and aerodynamics (PhRMA, 2016; Singh et al., 2013). That being said, an MPC is computationally more expensive and complex to implement in comparison to a traditional PID (proportional, integral, derivative) but it can achieve better closed loop process performance. Given that the implementation of control to the pharmaceutical industry is still nascent, it is an open area of research in terms of deciding many fundamental questions such as the choice between PID and MPC. The main complexities that are associated with this field are integration of commercially available software and hardware, data availability, collection and communication, and control loop implementation.

Pharmaceutical industries currently face a host of problems. Some of these are the high cost and the great lengths of time involved in drug development (approx. $2.87 billion; 10–15 years) (Dimasi et al., 2016), reduced effective patent life, higher regulatory constraints and relatively inefficient quality by testing (QbT) based batch product manufacturing. Automation has been the direction taken in recent years to address these problems as it promises to face these challenges more efficiently (Singh et al., 2014a). The fact that continuous processes can be run at steady state makes it more amenable to classical process control methodologies. This means that manufacturing processes can be more reliable and robust. Additionally, since continuous processes achieve steady state in just a few minutes it enables true Quality by Design (QbD) based manufacturing. In recent times, there has been a growth in interest in pharmaceutical industries to use inline/online process monitoring and efficient control methodologies to establish QbD based manufacturing for the next generation of pharmaceutical products. Given that this is the case, the implementation of control

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methodologies in pharmaceutical industries, especially in solid oral dosage forms, is still a virgin territory, thus making this an exciting research area (Ierapetritou et al., 2013). The traditional batch manufacturing paradigm is still used even though it has a number of disadvantages including a larger equipment footprint, higher equipment and operational costs, poorer controllability, and lower product quality (Singh et al., 2012a).

The fact that control is a neophyte area of research in the pharmaceutical industry also means that it is accompanied by number of challenges in its actual implementation. The standard existing control platforms do not take into account many characteristics of the continuous manufacturing pharmaceutical plant. Even if these challenges are navigated there is no standard communication protocol between the control platform and the pharmaceutical equipment, thus introducing another element of complexity in the data communication. The lack of data availability is also a problem in the case of conventional pharmaceutical manufacturing. Real-time accurate measurements for tablet CQAs are still not fully established in industry and progress is still being made in this field. That being said the advantages of using a control system outweigh the disadvantages.

An understanding of the process remains fundamental to establishing a robust control design and implementation. Extensive model-based (Barrasso and Ramachandran 2012; Barrasso et al., 2013; Sen et al., 2012, 2013, to name a few) as well as experimental (Portillo et al., 2010; Vanarase et al., 2010; Vanarase and Muzzio, 2011) studies have been conducted to understand the continuous tablet manufacturing process. Few attempts have also been made toward the design and implementation of a control system for the tablet manufacturing process (Bardin et al., 2004; Gatzke and Doyle, 2001; Pottmann et al., 2000; Ramachandran and Chaudhury, 2012; Sanders et al., 2009; Singh et al., 2014b, 2013, 2012a, 2010). However, no experimental attempts have been made to implement an advanced process control strategy within the tablet press to control tablet breaking force and weight simultaneously.

In this manuscript, the work is oriented towards establishing a new robust methodology for controlling the important critical process parameters (CPPs) and tablet CQAs, namely tablet breaking force and weight, through an advanced multi input multi output (MIMO) cascade MPC based strategy. A 2 × 2 MPC was implemented on the tablet press, which is part of a direct compaction line. OPC (OLE for process control) communication and a standard control platform have been used to control and close the loops. This controller is used in cascade configuration with a master tablet weight controller. Weight data was obtained through a novel weight measurement strategy that has been explored as a proof of concept.

2. Direct compaction continuous manufacturing process

2.1. Pilot-plant

The experiments make use of the continuous direct compaction tablet manufacturing pilot-plant that has been installed and situated at ERC-SOPS, Rutgers University, USA. A snapshot of the plant is shown in the Appendix (Fig. A1). The construction of the plant uses three levels to take advantage of gravity for material flow purposes. The top level is designated to powder feeding and storage, while the middle layer is assigned to the task of de-lumping and blending, the bottom floor is used for compaction. Each level spans an area of 10 × 10 feet. The equipment present in the lab includes three gravimetric feeders with the capability of expansion. Following the feeders, a co-mill is integrated for de-lumping the powders as mentioned before and creating contact between the components. The lubricant feeder is added after the co-mill in order to prevent over lubrication of the formulation in the co-mill. All these streams are then connected to a continuous blender to create a homogeneous mixture of all ingredients. The exit stream from the blender is fed to the tablet press via a rotary feed frame. The powder blend fills a die, which is subsequently compressed in order to create a tablet. This plant is modular in nature, thus, enabling the use of equipment in different combinations specific to the required experiments.

2.2. Compaction process

The compaction process essentially involves the conversion of a formulation that is in powder or granule form to a solid form through the application of force. More than 70% of all pharmaceutical products sold worldwide are manufactured using a rotary tablet press (Mendez et al., 2010). This process is mechanistically similar to roller compaction in that it exerts a force that is greater than yield stress of the material due to which, through sintering, forms a compact solid. The critical quality attributes that are normally monitored for this unit operation are tablet weight, tablet breaking force, dissolution and porosity. The process is complex and involves a myriad of variables and mechanisms that go into creating the tablets.

For the compaction experiments, API, excipient and lubricant were pre blended using a batch blender before being manually fed into the tablet press hopper. The single sided rotary tablet press has been used in the experiments. Tablet press parameters were monitored and controlled in DeltaV (Emerson) through OPC connection. The key parameters are highlighted in Table 1. Circular tablet punches with a diameter of 12 mm were used. Tablets were collected in a container placed on a catch scale in order to monitor the tablet weight in real-time.

3. Materials and methods

All the experiments were conducted using a blend with a composition of 89% lactose monohydrate (excipient), 9% acetaminophen (API) and 1% magnesium stearate (lubricant). The blend was prepared in a Glatt batch blender run at 25 revolutions per minute (rpm) for 30 min with a layered loading order to ensure that thorough mixing is achieved. The maximum capacity of each batch was of 7 kg, so multiple batches had to be prepared throughout the experiments. Most tablet press parameters were kept constant throughout the experiments unless otherwise needed as part of study. The parameters and their values are presented in Table 1.

4. Integration of control hardware and software

The communication between the control platform (DeltaV (Emerson)) and the tablet press unit takes place in a local area network through OPC protocol. In order for the connection to be completed there must be an OPC server installed on each end (tablet press and control platform) and an OPC client to interface the communication between servers. Process variables are commonly referred to as tags in OPC servers and clients. Advanced link tags must be configured in the OPC client in order to establish data flow between tags located in different servers.

A diagram of the control platform and the tablet press unit integration is presented in Fig. 1. Initially, the data from the tablet press is

Table 1
Key tablet press parameters.

Parameter	Availability	Value
Production rate	Set point & actual	8000–20,000 tablets/h
Turret speed	Actual	Dependent on production rate
Feed frame speed	Set point & actual	30 rpm
Main compression force	Set point & actual	Controlled
Pre compression force	Actual	Controlled
Main compression height	Set point & actual	Manipulated
Pre compression height	Set point & actual	4.05 mm
Fill depth	Set point & actual	Manipulated