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The transition from batch to continuous manufacturing for tablet manufacturing – performance comparison and control system review

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Abstract. The pharmaceutical industry is motivated to improve tablet productivity in order to adapt to the expanding drug market. One innovative way is the transition of the traditional batch tablet manufacturing process to a continuous process. This paper aims to review the performance of continuous tablet manufacturing processes. From the comparison of continuous to traditional batch processes, the continuous tablet manufacturing process demonstrates improvements in production flexibility, robustness, and ultimately process profitability. The continuous process is proven to mix drug particles with more evenly distributed size and less segregation resulting in tablets with better quality compared to the traditional batch process. The improvement on the continuous tablet manufacturing process requires robust control system for process automation to counteract process noise and disturbances in process feed. A well-tuned Proportional Integral Derivative (PID) control is sufficient for the process to produce a desirable product. Developing a new algorithm for model predictive control (MPC) and enhancing the control system with MPC-PID control can further improve the system performance. Overall, the transition from batch to continuous tablet manufacturing is supported by pharmaceutical companies as well as organizations like Food and Drug Administration (FDA).

Keywords: batch, continuous, tablet manufacturing, process control.

1. Introduction

Although the process of drug design has been evolving in the pharmaceutical industry, the drug manufacturing process has not been changed much in the last 50 years [1]. The majority of drugs have been manufactured in batch processes. In recent years, with increasing drug demand especially during pandemics, companies and institutions are keen on transitioning batch tablet manufacturing to the continuous process. Orkambi, the first drug that FDA has approved to be manufactured in the continuous process, is an example of a successful transition from batch to continuous tablet manufacturing process [2].

With only batch processes, the pharmaceutical industry has been identified as an industry with limited flexibility and lack of robustness [3]. The process can produce batches of tablets of poor quality which would cause a shortage of certain drugs on the market. Continuous tablet manufacturing provides an innovative solution to this current situation in the pharmaceutical industry. Like many other industries that have already adapted continuous manufacturing processes including oil and most food industries,

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the transition from batch to continuous industry provides benefits like shorter production time, less waste generation, and smaller production scale hence a lower cost with higher profit [4]. However, pharmaceutical industry consists of strict specifications and tablet manufacturing in-process quality analysis can be difficult to design, transition to continuous process with both regulation and technology restrains can be challenging.

The transition from batch to continuous operation is switching each individual batch operating units to continuous and connecting these units as building blocks of one continuous process. Since the traditional batch process has been a mature technology in pharmaceutical industry and most of the drugs are still produced in batch processes, the performance of newly developed continuous process sometimes is not as desirable as current batch process. This paper demonstrates the advantages and disadvantages of switching batch to continuous tablet manufacturing at current state by comparing both types of tablet manufacture processes to understand differences which would help better improve the innovative continuous process at specific aspects.

For drugs produced by continuous processes to meet specifications, developing a robust control system is required. With the help of process analytical technology (PAT) and model-based process design, tablet manufacturing has taken a huge step catch up the modernisation of pharmaceutical industry [5]. Monitoring of drug particles in continuous tablet production is still very different from tracking streams in other industries. Each operation unit requires different characterisation method. Due to the complex dynamics, some control strategies are not as effective in continuous tablet manufacturing processes. This paper aims to review algorithms of which can be effectively applied to continuous tablet manufacturing. Developing a suitable algorithm for system to manipulate input and achieve a stable and robust system behaviour is crucial.

2. Literature review

2.1. Batch and continuous comparison

Comparing to traditional batch tablet manufacturing process, continuous process offers more flexibility over operating conditions, raw material supply and product requirements. Traditional batch operation has the product of each individual batch unit tested, stored and transported to the following operating unit. From the production in the first batch to the last would take months of time, potential active pharmaceutical ingredients (API) degradation could happen in storage and consequently, the batch would be disposed of causing huge profit loss. Segregation is also likely to happen during transport processes causing undesired particle distribution which affects the final tablet dissolution and stability issues [3].

A quasi-continuous granulation and drying process was developed by Betz et al. [6]. The process introduced several parallel fluidised bed drying columns. The combination of batch mini sections creates a quasi-continuous process. Quality control can be implemented by monitoring an individual dryer power consumption. Since batch equipment is widely available and small-sized batch production is well established, the process provides a smooth transition from batch to a continuous process. The quasi-continuous process has a similar yield to the batch process as well as a more effective control system.

For the direct compaction process, batch and continuous process are both examined by Karttynena et al. [7]. The experiment was done on different raw material formulation and particle property. After analysing the final tablet product weight distribution, API percentage and tablet tensile strength, continuous direct compaction shows a general better compression performance. For long time operation, continuous process manufactured product with more steady quality whereas product from batch process has fluctuating quality over time and some of the batches exceeded the quality limits resulting wasted batch. The study also shows that the continuous process is more efficient in processing raw materials with poor flow qualities. For the experiment with low API content, batch has slightly better performance than continuous process since the continuous process is struggling to maintain the low API flowrate proving that it is essential to improve the continuous equipment with suitable dimensions.

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Another study on comparison of batch and continuous manufacturing of ethenzamide by Matsunami et al. also shows better product quality with continuous process [8]. Both batch and continuous processes use high shear granulation. With analysed result from scanning electron microscopy (SEM), less segregation was found in product from continuous process and particle size distribution in granules from continuous process are more evenly distributed. However, continuous process in this case has a lower production yield than batch process. Since continuous system used in this study has a mixing process separated from the rest of processing units and the whole process was operated manually, the continuous operation experienced a significant amount of material loss at the start up (2.04%). The continuous process can be further reinforced with modified process flow and a robust control system to achieve desirable performance.

Economic analysis on switching batch to continuous pharmaceutical process is also an important aspect to investigate. For tablet production of 2000 tons per year, the comparison was done on well-established batch process from Novartis and continuous process from the Centre of Continuous Manufacturing [9]. Since the continuous process, in this case, has not been developed at an industrial scale, the economic analysis was mainly based on estimations and assuming the recycling in the continuous process is equal to that of the batch process. It was found that capital cost of continuous process has a 20 to 76% of decrease and operating cost has 40% decrease to 9% increase. In the best-case scenario, the continuous process gives a 9 to 40% of saving comparing to batch process. Continuous process is operated at lower cost even it is assumed that the yield is 10% lower. The savings are mainly from plant capital and labour cost. Another study on simulation of investment in continuous oral solid dosage (OSD) pharmaceutical product production in the USA also shows a higher NPV than batch process [10]. Above studies demonstrated solid economic potential of transition to continuous pharmaceutical process.

Continuous pharmaceutical manufacturing pilot plant on both small molecule API and OSD was analysed by Testa et al. [11]. In comparison to batch processes, the pilot plant demonstrates high production flexibility and economic profit by addressing quality by design (QbD) strategy and demonstrating continuous pharmaceutical plant operation. The summary of the second International Symposium on the Continuous Manufacturing of Pharmaceuticals in 2016 suggests that the regulatory agencies encourage the shift from batch to continuous pharmaceutical process where academia have made many contributions to realise the shift [12]. To adapt the production requirements and regulatory changes, continuous process appears to be a promising advancement to traditional batch process which can be proved by comparisons on process performance and economic analysis stated above.

2.2. Continuous process control

Process control is required for every pharmaceutical manufacturing plant. A control is to manipulate the system variables to achieve the desired product quality in response to raw material property change, operation environment disturbances and regulation change. Pharmaceutical industry control strategies can be categorised into 3 levels of control: recipe control, pharmaceutical control and engineering control respectively [3].

Level 3 recipe control is manipulation of process parameters based on product specification and raw material characterisation. Quality by testing (QbT) is introduced by extensively testing final product of process to understand effect each parameter involved on product quality [13]. Level 3 recipe control needs to be carried out repetitively and it provides limited flexibility over range of parameters. It is often applied by batch processes, since continuous process control requires more flexibility on process operation and continuous control needs multivariable operation control which recipe control is unable to provide.

Level 2 control has all critical operation unit specified in a design space. The design space is restrained by critical process parameters (CPPs), a multivariable constrain, so that the final drug product meets the quality specifications. All non-critical operation unit can still adapt level 3 recipe control. Analysing and understanding the effect of changing each or a group of parameters on the system reduces the need for extensive final product testing [3].

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Level 1 control requires engineering knowledge on control model system and algorithm design. Traditional batch tablet manufacturing process has each unit operation including upstream API synthesis, crystallisation and downstream mixing, granulation and tablet compression. Continuous process connects each operation unit to one process. Since the output of a previous unit is the input of the following unit, no storage and in-process testing are required. To regulate system flowrate and output characteristics, a control system needs to be in place for process automation and product quality control.

A tablet downstream manufacturing control system shown in Figure 1 is proposed by Malevez and Copot from blending to final tablet compression step [14]. This control system consists of close loop and cascade PID control. Simulink simulation results prove a robust control system as the process value fluctuates within the acceptable range around the set point. However, the control system proposed only consists of PID controllers. A study based on continuous pharmaceutical manufacturing pilot plant shows that developing model predictive control (MPC) algorithm can further improve the control system performance and makes the process more adaptable to regulation changes [15]. Plant operators will also benefit from straightforward control system tuning and operation [16]. MPC control system design often requires a feasible system model. Pharmaceutical processes always have complex process dynamics and reaction kinetics which makes system modelling less practical. Study on MPC control of single continuous stirred tank reactor (CSTR) reaction with complex reaction kinetics shows that recurrent neutral networks (RNNs) combined with MPC control results a stable close-loop performance even if the process dynamics is not perfectly described [17].

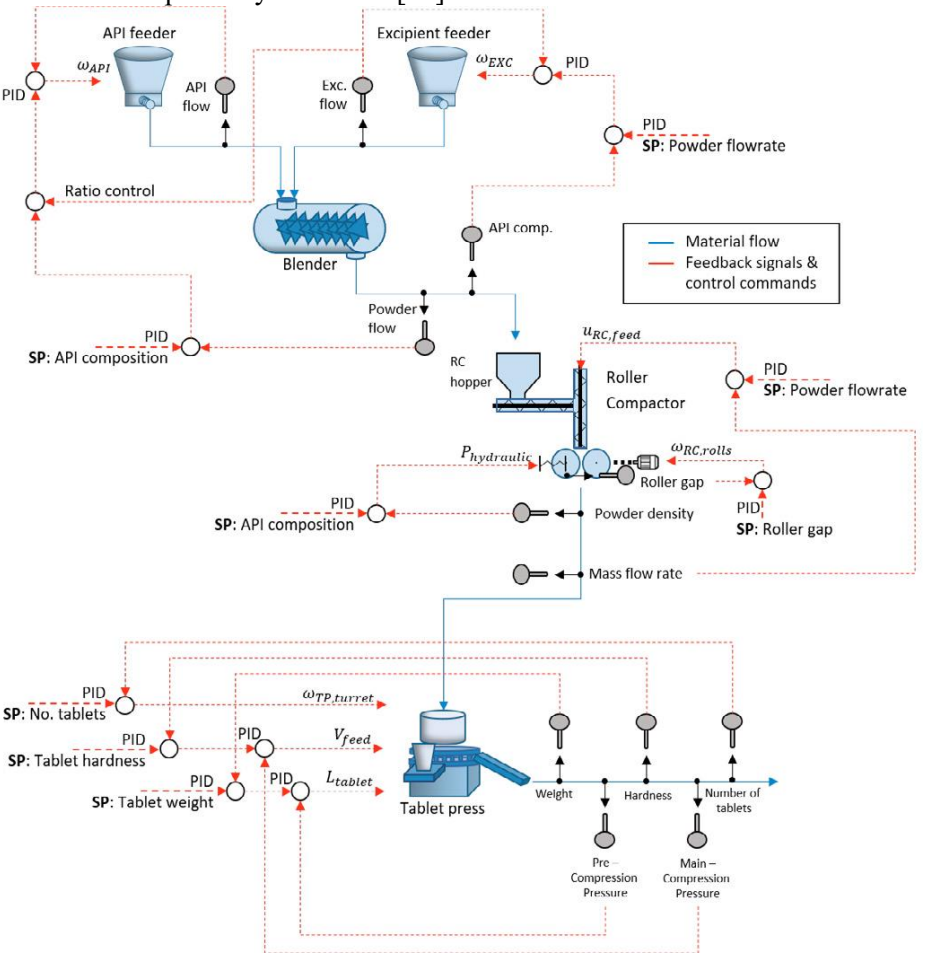

Figure 1. Proposed Proposed continuous tablet manufacturing process control system in MATLAB Simulink.

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3. Discussion

Both comparisons of batch to continuous tablet manufacturing processes focused on downstream processes. The comparison primarily based on granulation results from particle engineering point of view. The most benefits for particle quality with elimination of storage and transportation from batch to continuous process are more evenly distributed particle size and less segregation after granulation. The low yield result in continuous process was unexpected, but the study has explained that lack of control system in continuous process would give slow start-up resulting waste product. The comparison of batch and continuous performance in slow processes may not be significant, but for very fast processes, continuous process provides homogeneity as batch process is unable to provide [18].

Like control systems in other continuous manufacturing processes, continuous tablet manufacturing process control system are designed and modelled with software like MATLAB Simulink before applying to the actual process. The model assesses the system response to noise, disturbances and change in set point. Tuning for control system requires many empirical relations with respect to different system behaviour. Even with empirically calculated values for controller, extensive manual tuning is required for optimisation of control system. After applying the modelled control system to real process, some unexpected disturbances would still happen which requires more in-site open loop controller tuning. Overall, control system consists of multivariable manipulation to reach process automatic response to fluctuations.

One effective way of tracing raw material in process is to use residence time distribution (RTD) method. RTD indicates the material distribution throughout the continuous system. Traceability of materials in system deeply relies on accuracy and frequency of sensing technics [19]. Since characterisation of system output needs to be quantified, spectroscopy technics are developed in many groups to calibrate against different material stream properties including blend potency and extent of segregation [20]. Further calibration and sensor development are required to give a more accurate system response to the control system.

Continuous tablet production is undeniably a major trend in pharmaceutical industry but challenges of transition from batch is also predicted. According to industry and market research investigated by Cole and Johnson, besides process control design, the major challenges identified are on technologies and research burden since pharmaceutical scientists are more familiar with batch processes. Advanced process understanding on homogeneous flow in continuous process is essential [21]. Existing batch equipment may also be a reason for companies to stay in batch production for economic considerations. Overall, with development of continuous process and support from both research and regulatory institutions, the solutions for challenges are being discovered. Large pharmaceutical companies are dedicating effort on continuous drug production [22] [23].

4. Conclusion

The continuous tablet manufacturing process enhances the pharmaceutical industry with improved flexibility, robustness, and product quality. Pharmaceutical companies benefit from smaller scale production plants, shorter production periods, less waste, and less labour involved in the production process where all the benefits would ultimately lead to a more profitable process to invest. During the recent pandemic, it appears that society requires a flexible pharmaceutical industry to adapt the increase in market demand, therefore continuous process can be an innovative and robust solution. Comparing both unit and overall continuous process operation performance, it was found that the continuous process manufactures tablet product with steady quality in long time operation but some unmature continuous process without proper control system have lower yield comparing to that of a batch system. Economic analysis on continuous pharmaceutical process suggests promising savings regarding both capital and operation costs. With the help of PAT, the continuous system behaviour can be monitored and analysed. Designing a control system can counteract the process fluctuations on feed and noise from environment. Common PID control has been proven to be robust in both simulation and actual experiment, but control system can be further improved by introducing model predictive control algorithm and forming an MPC-PID hybrid control. Continuous tablet manufacturing process is studied and constantly improved by

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companies and institutions. Although this technology has only started to develop in the last decade, it is considered a huge step for the pharmaceutical industry to achieve modernization of manufacturing.

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