Aliyansah. *J. Sci. Technol. Res. Pharm.* *(2022) 2: (1)p38-44*
https://doi.org/10.15294/jstrp.v2i2.68836
ISSN 2776-0685

Journal of Science and Technology Research for Pharmacy

RESEARCH Open Access

A Review of Continuous Manufacturing in Pharmaceutical Process Monitoring

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ABSTRACT
This review explores continuous manufacturing (CM) process monitoring in the pharmaceutical industry and its advantages over batch processes. The case study focuses on CM production of solid dosage forms, using a water-based wet granulation method. The research proposes a monitoring strategy through in-process control (IPC), process analytical technology (PAT), and critical process parameters (CPPs). The study demonstrates that the CM process is robust and provides satisfying results, with critical quality attributes (CQAs) meeting target specifications. The role of IPC and PAT in ensuring product quality is highlighted, with IPC used to monitor and adjust processing operations, while PAT enables real-time monitoring of drug content. The advantages of CM include improved product quality, agility in drug development, elimination of scaling-up challenges, and reduced environmental exposure. However, implementing CM requires a systematic approach and significant capital investment. The review concludes that CM offers benefits despite the challenges and presents a promising approach to modernizing pharmaceutical manufacturing.

Keywords: continuous manufacturing, in-process control, process analytical technology, critical process parameter, critical quality attribute

1. INTRODUCTION

For more than a half-century, pharmaceutical industries have been dominated by “batch process”. It is described as a multi-step process requiring large-scale equipment resulting in a lengthy process. Depending on the type of dosage form, the unit process operations can vary. For solid dosage form manufacturing alone, a series of unit processes may include dry blending, wet granulation, drying, dry milling, final blending, tablet compaction, and packaging. In-process control (IPC) is an important testing activity which is performed between unit operations to ensure product quality, as depicted in Figure 1. However, in batch processes, IPC is often carried out offline, which means the process is halted until the in-process products meet quality specifications. This could result in time-consuming manufacturing processes. Furthermore, the testing is done by sampling suggesting a portion of batch is left untested.

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https://doi.org/10.15294/jstrp.v2i2.68836
ISSN 2776-0685

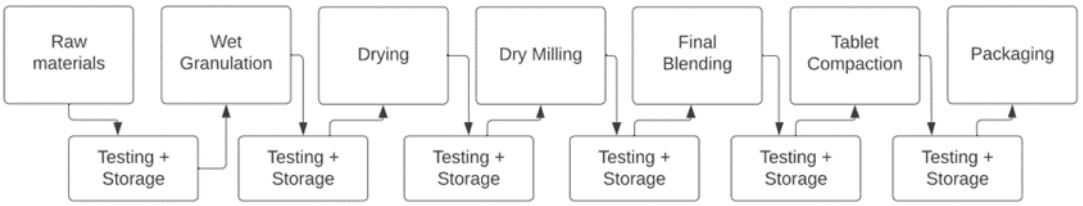

Figure 1. A diagram flow of typical batch process in solid dosage form manufacturing in pharmaceutical industries.

Controlling process parameters is an essential step to meet the IPC specifications and prevent product rejection. Specifically, for parameters identified as critical process parameters (CPP), it is necessary to consistently maintain and monitor their values due to their significance impact on critical quality attributes of the drug (efficacy, safety, and overall quality)[1].

To enhance the pharmaceutical quality, Food Drug Administration (FDA) encourages the implementation of emerging process technologies, including continuous manufacturing (CM)[2]. This initiative is further reinforced by the International Conferences for Harmonisation, which has published guidelines[3] on continuous manufacturing for drug substances and products.

The significant contrast between CM and traditional batch methods can be observed in the approach of analysis. In CM, inline and online analysis are employed to ensure product quality. The process is known as process analytical technology (PAT), a technology which possesses the ability to analyse and control a manufacturing during the processes in a thorough and timely manner[1]. PAT incorporates non-invasive analytical instruments, such as Near Infrared (NIR), Middle Infrared (MIR), Raman, and Focused Beam Reflectance Measurement (FBRM) which are frequently integrated into the process equipment[4]. Therefore, the product quality could be directly monitored during the process and enables real-time release testing (RTRT).

The implementation of PAT in CM offers significant advantages in terms of both process efficiency and quality improvement.it reduces the processing time and facilitates the quality assurance of almost all final products. Furthermore, CM has been reported to address issue related to powder segregation in tablet dosage form manufacturing, as suggested by Ervasti et al[5].

This review aims to discuss the case study of continuous manufacturing (CM), emphasizing the importance of in-process control (IPC) and process analytical technology (PAT) in CM. Furthermore, it aims to highlight the benefits of implementing CM compared to batch production methods.

2. CASE STUDY OF CONTINUOUS MANUFACTURING PROCESS MONITORING

In this section, a review of the continuous manufacturing (CM) process and its monitoring is presented, based on a research study conducted by Roggo et al[6]. The objective of their research was to propose a monitoring strategy for the CM production line. Additionally, design of experiments (DoE) was employed to assess the process's robustness.

https://doi.org/10.15294/jstrp.v2i2.68836
ISSN 2776-0685

2.1. Summary of Process Production and Methods

Water-based wet granulation method was employed in this continuous manufacturing process where the formula incorporated 40% active pharmaceutical ingredients. The formula and equipment were provided by Novartis Pharma AG Switzerland[6] and the modified-simplified production flow is presented in figure 2.

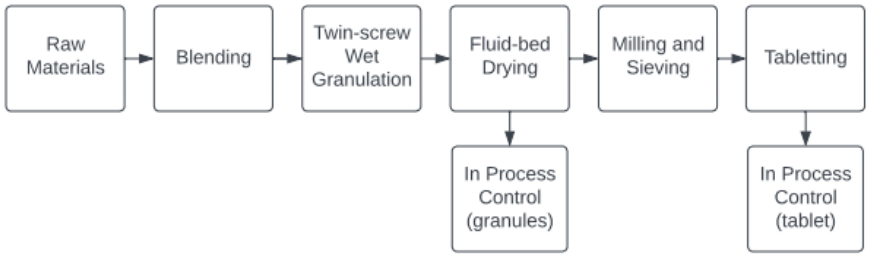

Figure 2. The flow of continuous wet granulation process and main operating units. The chart is simplified and modified from Roggo et al[6].

The process was initiated by blending 60 kg of powder with a Pharma Telescope Blender machine twice. In between blending process, sieving process was performed to prevent agglomerates. The powder was granulated by Twin Screw Granulator (TSG). The design of experiment (DoE) factors was applied in this phase: Wet granules water content, granulator screw fill level, and granulation shear force. Three different levels of each factor were investigated; in total, 11 experiments of DoE were performed. The wet granules then were dried in the continuous fluid-bed dryer (FBD) directly connected to TSG before sieved to improve the granules flow and compressibility properties. Finally, the granules were compressed in a rotary tablet press producing final products[6].

Monitoring of process was carried out by attempting in-process control (IPC) within specific time intervals. Critical quality attributes (CQAs) were the subject of IPC inspection. During blending and drying, loss on drying (LoD) and particle size determination (PSD) were inspected while during tabletting generally the physical characteristic of tablets was evaluated namely, tablet weight uniformity, thickness, hardness, friability, and disintegration time tests. Additionally, tablet's content aspect was also inspected. To understand the correlation between CQAs, cross-factor interactions were attempted [3].

The API content was monitored by process analytical technology (PAT) using near-infrared spectroscopy (NIRS) where its three probes were installed on FBD, tablet feed frame, and finished tablet section. NIRS method validation and PAT sensor calibration were carried out before the conducted experiment to ensure the data output reliability. Moreover, 14 critical process parameters (CPPs) were documented and analysed with the univariate and multivariate methods throughout the process[6].

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2.2. Summary of Results

Three monitoring strategies were conducted: IPC, PAT, and CPPs. The IPC values showed all the DoE runs provided satisfying results as the CQAs remained within target specifications. Even though variations were observed, it was considered as not-critical parameters. Afterwards, DoE statistical analysis was performed to investigate the significance of variance and the interactions between factors. The most noticeable result was that the shear force was highly correlated with PSD as the score was >0.7. Regardless of the other correlation values, the tablets passed the uniformity test, a critical product attribute, and the process was considered as robust[6].

The NIRS method was validated using granules with 70%, 100%, and 130% of the claimed dosage and the model was verified by cross validation. The validity of the overall process was valid, and the steps were followed up by API content monitoring. Overall, from 11 runs, it was concluded the content of API was very constant. Likewise, in intra batch variability, the process produced low RSD as well with less than 3%; however, during the process in DoE experiment, high RSD value of API content was observed after the FBD stage where the maximum RSD was reported at 17.6%[6]. Other study involve API concentrations in FBD equipment reported lower values at 3%[7] while FDA guidelines required the percentage to be lower than 6%[8]. The unsynchronized probe head – granule sizes and the variabilities between chambers of the dryers were believed to be the reason of excessive RSD percentage in Roggo et al study[6]. They also suggested that by improving the probe position or the synchronization of measurement within the process could increase the precision of measurement improving the RSD level[6].

The first CPPs parameter analysis was carried out by univariate analysis. The correlation between supplementary materials and the drying parameters (inlet, outlet, airflow, temperature) were assessed. Next, the three process units (feeding, granulation, and drying) were identified and written univariate. From the evaluation of the analysis, it was reported that a univariate control chart provided numbers of the varying result between runs in each parameter for visualisation. Hence, a univariate control chart could be utilised to detect process variation[6].

Multivariate analysis proceeded as the second analysis. Two different approaches were attempted: Principal Component Analysis (PCA) and Partial Least Squares (PLS) regression (Batch-MSPC approach) using two different data sets, steady-state process and complete monitored process. However, since the entire monitored process containing stops and start-up processes highly influenced the PCA statistical method, the PLS analysis was focused more on the steady-state data process. The statistical analysis then reported almost no significant differences in observation, suggesting that batch-MPSC was a reliable tool in this process monitoring experiment[6].

In summary, the study by Roggo et al. has demonstrated the framework of monitoring strategies in CM through IPC, CPP, and PAT. Furthermore, from the DoE experiments it was reported that all IPC results met the specifications and the PAT probes provided stable results with no critical variations was observed[6].

THE ROLE AND IMPORTANCE OF IPC AND PAT ENSURING THE QUALITY OF PHARMACEUTICAL PRODUCT

In a drug manufacturing process, most finished products are only tested by sampling. Therefore, good manufacturing practice (GMP) was required to minimise the risk because it emphasises the quality built into the product and processes[9]. IPC is a manifestation of the application of GMP in drug manufacturing that ensures the quality of the product by assuring that the production steps meet the required specifications before being further processed. The IPC in the process has three scopes[10], (1) to monitor and adjust processing operations, (2) to confirm that process operations have gone as expected through in-process testing, (3) to redirect operations according to need based on the result of the in-process essays. Furthermore, IPC helps the process be within the operational space, determined by Quality by Design (QbD)[11].

Most IPC for assay testing is accomplished out-process or off-line. However, process analytics technology (PAT) enables IPC assay to perform in real-time. Furthermore, PAT encompasses wide-range characteristics such as measurement system, real-time collection, broad application to small drugs synthesis, a direct connection between process development activities and QbD, improvement of process understanding for continuous improvement, real-time product release for commercial products, integration with plant-enterprise automation and information technology (IT) infrastructure[12].

THE ADVANTAGES/DISADVANTAGES OF A CONTINUOUS MANUFACTURING PROCESS RELATIVE TO BATCH PRODUCTION PROCESS

The continuous manufacturing process is a complex-integrated process compared to batch manufacturing. In the batch type, the materials are processed step by step, where in-process control is performed for each test. If the in-process materials are out of specification, they may be discarded for quality purposes. However, in CM, each process step is directly linked, and the materials are continuously processed until they become finished products. Each processing step requires reliable equipment to enable production products within acceptable characteristics quality[13].

CM offers agility in the drug development phase. Scaling from small scale to commercial ones is often a problem in batch manufacturing because of equipment capacity issues. On a commercial scale, often, the amount of material is much greater than the laboratory scale. Hence, the pharmaceutical companies have to adjust their formula in terms of production size. In addition, drug authorities require a stability test if the scaling process is performed during drug development, prolonging the launching of new drugs to the market[14]. However, as the equipment in CM is interconnected, it is possible to develop from a small volume in the development stage to commercial volume in the same equipment. In addition, the holding time between processes is also eliminated in CM, reducing the environmental exposure of the drug leading to drug quality improvement[2]. CM also requires the utilization of PAT. Compared to the batch processes that rely on sampling to ensure their quality, PAT assures the product by monitoring its quality in real-time. Therefore, enabling production to be stopped in time. Consequently, increasing the product quality.

The challenge of CM implementation lies in developing an adequate control strategy of production. Considerations that are unique to continuous production should be evaluated, as the

process, product, or environment could be varied over time[2]. Compared to batch-based that could adjust each production, controlling CM product's quality is complex. As a result, to accomplish CM in the pharmaceutical industry, a systematic approach is needed. Moreover, big capital investment is required as the CM has not been utilized widely throughout the world. Another barrier that hindered manufacturers from adopting the technology is regulatory uncertainties. The regulators should provide harmonization guidelines on CM to facilitate the implementation of CM in industries[15]. Nevertheless, it is reported that seven big pharmaceutical companies have invested in the continuous process[16], suggesting that the trend towards a CM in pharmaceuticals are on its way.

CONCLUSION

The process monitoring research conducted by Roggo et al.[6] has demonstrated an excellent CM monitoring strategy where multiple strategies might be applied. In addition, the role of monitoring is critical in pharmaceutical production maintaining product quality. Moreover, the CM process offers relatively benefits over traditional manufacturing methods even though serious efforts to overcome the challenges of its implementation need to be done.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

AUTHOR DETAILS

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