Manufacturing of a Continuous Line of Salbutamol Tablets Through the Methodology of DMADV

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Abstract

This project aimed to enhance the production process of salbutamol by designing and implementing a continuous production line using the DMADV methodology. The study objectives were to establish proper visualization of the interconnections of all unit operations, measure critical process parameters using the Pareto diagram, and develop an optimized design for salbutamol tablet production through verifiable experimental design methodology. Results suggest that the optimal conditions for continuous production of salbutamol tablets, using the wet granulation method, are a temperature of 85°C, mixing speeds of 630 nm, chopper speed of 250 nm, and a time of 10 hours. The project benefits include the design of a more efficient and cost-effective continuous production process for salbutamol tablets, enabling faster medicine distribution and improved respiratory health. Furthermore, the DMADV methodology employed in this study contributes academically to all researchers seeking to work on a continuous manufacturing approach..

Introduction

Pharmaceutical production is a heavily regulated field that enforces stringent quality control standards for medicines. Although most pharmaceutical companies rely on batch manufacturing, a growing trend towards continuous pharmaceutical manufacturing has emerged in recent years due to the widespread demand for specific medications [1]. This is because batch processes in manufacturing present a challenge, as they require quality and uniformity testing for each batch before future batches can be produced, resulting in downtime. In batch processes, machinery must be stopped and recalibrated between batches, which also cause downtime, and storage costs are higher for large batches of the same product [2]. On the other hand, continuous manufacturing is more productive, as there is always a production line running, making the process more time-efficient. This type of process also reduces energy needs, helps increase productivity, and minimizes the amount of overall waste, resulting in lower expenses, more benefits, and fewer opportunities for contamination. Furthermore, since continuous processing involves fewer people in the production process, the risk of human accidents is also decreased [3].

Background

Mixer granulators have a stirrer that allows particles and liquids to be mixed to achieve granulation, even if it is not the intended outcome; mixer granulators have multiple applications in industries such as ceramics, pharmaceuticals, agrochemicals, and detergents, and offer various advantages. The granules generated in mixer granulators might not have the same level of sphericity as the ones produced in tumble granulators, but they are usually denser due to the intensity of agitation, the size and density of the agglomerate are determined by regulating the quantity of liquid phase and the degree and duration of mixing. Typically, mixers require less liquid compared to fluid bed granulation and tumble due to the greater compaction and kneading action [4]. An example of this equipment is shown in Figure 1.

Figure 1
Vertical high-shear continuous granulator [4].

In addition, a fluidized bed dryer is used after completing the granulation operations to fulfill its function. Continuous plug-flow fluid beds are designed with a specific trajectory for solid flow through the bed, with deflectors to avoid or limit horizontal mixing of solids. This arrangement allows for a narrower distribution of solid residence time. The shape of the bed can be rectangular or cylindrical, and the moisture and temperature of the solid material will vary along its path through the bed, allowing it to approach equilibrium with the drying gas [4]. Figure 2 illustrates an example of a plug-flow fluid bed.

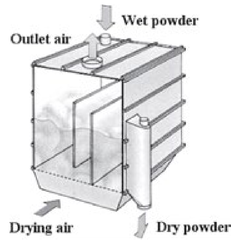

Figure 2
Continuous plug-flow fluid bed [4].

The cone mill (Figure 3) is widely used in the pharmaceutical industry due to its ability to separate lumps and disintegrate granules. This type of mill uses shear compression to break material in the space between the impeller and the screen. Feeding of products to the mill can be by vacuum or gravity, and the rotating impeller forces material outward to pass through the conical surface of the screen. Heat generation and solid material accumulation are minimal due to the short residence time of the material in the grinding chamber. Cone mills are available in different sizes and can be customized for use. In addition to size reduction, these machines can de-agglomerate, sieve, disperse, and mix [5].

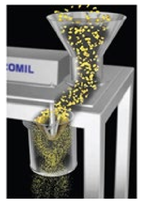

Figure 3
Illustration of co-mill overdriven [6].

On the other hand, continuous processes are a cost-effective alternative to batch processes, even for small processes, and can be used as a lean manufacturing strategy to reduce inventory and operating costs [7]. Implementing a manufacturing management philosophy for continuous improvement involves adopting a systemic approach to seeking improvements in the company's products and processes. Innovative techniques such as just-in-time inventory, total quality management, and flexible manufacturing systems must be integrated as an integral part of the continuous improvement process [8].

The DMADV methodology is a strategy used in Six Sigma that consists of five phases: Define, Measure, Analyze, Design, and Verify. This methodology emerged due to the need to improve the product or process design phase, as it has been demonstrated that making changes in this phase is much more economical than making them once the product is in production. Designing the product well from the beginning helps reduce manufacturing, assembly, service, and support problems [9]. However, the questions that must be answered in each phase of DMADV are different, as shown in Figure 4.

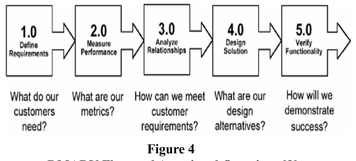

Figure 4
DMADV Flow and Associated Questions [9]

Problem

Despite the proven efficacy of Salbutamol as a bronchodilator in treating bronchospasms and its widespread use as a first-line treatment for asthmatic patients during and outside of crises on an international scale [10], the production of Salbutamol tablets still relies on batch manufacturing. This traditional approach to production often leads to typical challenges associated with batch processing, such as longer production cycles, increased variability between batches, and potential for errors during scale-up or equipment changeovers.

Methodology

A Six Sigma methodology with a DMADV approach was implemented to systematically and phase-wise achieve the research objectives. During the Define Phase, a CTQ (Critical-to-Quality) tree diagram was developed to identify critical parameters. A Measurement System Analysis (MSA) was performed using the Minitab software to ensure precise data collection. Once the critical parameters were determined, a Pareto Chart was created to measure their impact. The selection of design was based on the experimental objectives, favoring the Response Surface Method (RSM) and the specific analysis technique of comparing 'Two Processes'. In the subsequent Design Phase, all critical parameters of the continuous line were optimized, and factors were simultaneously tested and controlled. The development of formulations involved Design of Experiments (DOE) and statistical analysis. Finally, the Verification Phase established the desired control by employing the X-Bar control chart method for critical parameters in each operational unit. The chart included the lower control limit (LCL) and upper control limit (UCL) for data analysis.

Results and Discussion

The result of the Pareto diagram revealed that temperature, mixer speeds, chopper speed, and time data are utilized in the simulation of the continuous production of salbutamol tablets to comprehend and optimize the manufacturing process. In the Minitab software, different production configurations and strategies were experimented with, which can help improve product quality and reduce production costs, with the most relevant data presented in Table 1.

Temperature (°C)	Mixer speed (nm)	Chopper speed (nm)	Time (hours)	Production
50	630	250	6	1500
85	640	260	10	2500

Table 1
Data considered in experimental manipulation

The material input was set to be continuous at the feeder entrance, assuming a correct proportionality for the entire system, and this report describes the functionality of the continuous line. Additionally, the amount of mass input is important and should be balanced throughout the process. The figures displayed below (Figures 5 and 6) show surface graphs that illustrate how temperature, mixer speed, and chopper speed significantly impact continuous production at different time points.

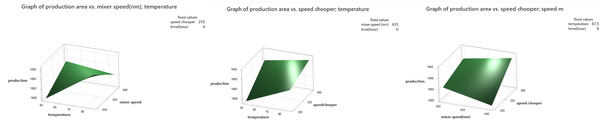

Figure 5
Graphical representation of RSM at minimum time.

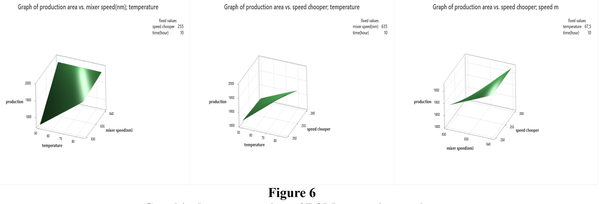

Figure 6
Graphical representation of RSM at maximum time

After the design process was completed, it was found that there were over 30 critical data points in the process. Therefore, the results were verified using the X-bar chart, which is a visual representation of the data collected during the production or manufacturing process of the product. As shown in Figure 7, it was determined that everything is stable and that no control point exceeds the established limits, meaning that the process is under statistical control. In other words, the data being collected during the process is consistent and predictable, suggesting that the process is functioning consistently and producing quality products.

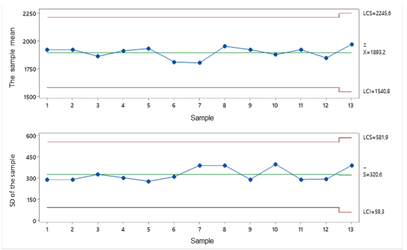

Figure 7
Control charts (XBar-S graph of production).

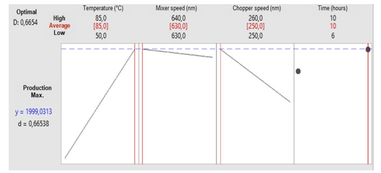

Figure 8
Optimal data for maximum production.

Overall, the results indicate that the conditions of 85°C temperature, 630 nm mixer speeds, 250 nm chopper speed, and 10-hour time are the most optimal for the production of salbutamol tablets in a continuous line using the wet granulation method, ensuring high-quality of the final product and efficient production in the process (Figure 8).

Conclusions

The study revealed that the optimal conditions for the process are a temperature of 85°C, mixer speeds of 630 nm, chopper speed of 250 nm, and a time of 10 hours. However, it's important to note that ongoing monitoring and adjustments may be needed to accommodate specific formulation requirements, equipment variations, and environmental factors. The project's limitation was the inability to modify the product formula, focusing solely on process manipulation. Nevertheless, it successfully optimized production times in a continuous process. These findings make a significant contribution to researchers and professionals interested in implementing DMADV-based continuous manufacturing processes. It is recommended that they follow this approach and consider implementing the proposed design in an actual production plant for further measurement and comparison of outcomes.

References

[1] Billups, M., & Singh, R. (2020). Systematic Framework for Implementation of Material Traceability into Continuous Pharmaceutical Tablet Manufacturing Process. Journal of Pharmaceutical Innovation, 15(1), 51–65 doi: 10.1007/s12247-018-9362-9

[2] Smith, J. (2017). The Pros & Cons of Batch Production - Global Electronic Services." Global Electronic Services. https://blog.gesrepair.com/2017/06/03/the-pros-cons-of-batch-production/

[3] Kochling, J. (2019). Q&A session with Jianmei Kochling. Homepage - Oxford Global. https://www.oxfordglobal.co.uk/wp-content/uploads/2019/10/Jianmei-Kochling-QA.pdf

[4] Green, D., & Southard, M. (2019). Perry's Chemical Engineers' Handbook, 9th Edition. McGraw-Hill Education.

[5] Metta, N., Yohannes, B., Kotamarthy, L., Ramachandran, R., Romañach, R. J., & Cuitiño, A. M. (2022). Continuous dry granulation. En How to Design and Implement Powder-To-Tablet Continuous Manufacturing Systems (pp. 93–118). Elsevier. doi: 10.1016/B978-0-12-813479-5.00014-8

[6] Comil - overdriven. (2018, septiembre 7). Ytron-Quadro (UK) Ltd. https://ytron-quadro.co.uk/products/quadro-comil-overdriven/

[7] Am Ende, D. J., & am Ende, M. T. (2019). Chemical engineering in the pharmaceutical industry. Chemical Engineering in the Pharmaceutical Industry, 1–17. doi:10.1002/9781119600800.ch51

[8] Cleland, D., (2007). Project Management: Strategic Design and Implementation, 5th Edition. The McGraw-Hill Companies, Inc.

[9] McCarthy, T., Daniels, L., Bremer, M., & Gupta, P. (2005). Six Sigma Black Belt Handbook (Six Sigma Operational Methods). The McGraw-Hill Companies, Inc.

[10] Olivera, N. D., Pardo, L., Monteverde, G., Saralegui, F., Kanopa, V., & Giachetto, G. (2021). Reacciones adversas por salbutamol en pacientes asmáticos: reflexiones acerca del uso en las exacerbaciones. Archivos de pediatria del Uruguay, 92(2). https://doi.org/10.31134/ap.92.2.5