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

Michael Santiago Rodríguez
Master of Engineering in Manufacturing Engineering
Advisor: Rafael Nieves, Pharm.D.
Industrial and Systems Engineering Department
Polytechnic University of Puerto Rico

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.*

Key Terms *— Continuous Production, DMADV Methodology, Salbutanol, Wet Granulation.*

PROBLEM STATEMENT

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 causes 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].

However, 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 [4], the production of Salbutamol tablets continues to rely on batch manufacturing.

Research Description

The statistical data from the World Health Organization [5] shows that asthma, a chronic respiratory disorder, affected 262 million people worldwide and caused 461,000 deaths in 2019 alone. In Puerto Rico, approximately 430,000 people suffer from asthma, accounting for 12.2% of the population, as reported by Medicina y Salud Pública in 2020 [6].

Therefore, it is important to understand and optimize the continuous manufacturing process of tablets, which involves granulation and sizing, tablet pressing, coating, and encapsulation. Granulation is the process where particles are

converted into larger, more robust agglomerates with good flow properties, improved compression characteristics, and uniformity. As there are different ways to develop the granulation stage, this study has considered developing a design based on the wet granulation process, which is the most commonly used process in the pharmaceutical industry.

To improve the previously mentioned production processes, a manufacturing process will be designed using the DMADV methodology. DMADV is a Six Sigma framework that focuses primarily on the development of a new service, product, or process, as opposed to improving an existing one; this approach, or acronym, consists of: Define, Measure, Analyze, Design, and Verify [7].

Research Objectives

The main objective of this study is the manufacturing of a continuous line of salbutamol tablets through the DMADV methodology. To achieve this objective, the following specific objectives have been proposed:

- To establish the proper visualization of the interconnection of all unit operations and automation without operator management using a project charter, as well as the critical parameters of each unit operation by creating a CTQ diagram tree.
- Measuring critical parameters of manufacturing processes using the Pareto diagram.
- Develop an optimized design for a continuous line of Salbutamol tablets production through experimental design methodology.
- Verify, through a surveillance system, the automated forward and backward loops using control chart.

Research Contribution

First, at the pharmaceutical and social standpoint, the design of the continuous line manufacturing process of salbutamol tablets through the DMADV methodology will contribute to the creation of a faster and more efficient production system of Salbutamol tablets. These tablets are a relief for all types of bronchospasms in bronchial asthma, chronic bronchitis, and emphysema, and help to relax the muscles of the airways leading to the lungs, improving the amount of airflow. In summary, this represents an increase in the distribution of tablets that help improve the health of people affected by these diseases. Therefore, the development of this study will indirectly help prevent and treat the symptoms of asthma.

Second, from a professional and academic standpoint, the benefit of developing this study is that the continuous manufacturing of Salbutamol tablets makes the production line more productive and efficient. This type of process also reduces energy requirements, helps to increase productivity, and minimizes overall waste, resulting in lower expenses, greater profits, and fewer opportunities for contamination, thereby reducing the risk of human accidents. Also, continuous manufacturing has the potential to increase cost savings by maximizing yield and minimizing batch losses caused by issues. By carrying out reactions on a smaller scale, only a small quantity of product is at risk of being lost in case of failure, which could result in significant savings in terms of both money and raw materials. Finally, this experimental design will be an academic contribution to all researchers who want to work on a continuous manufacturing approach using DMADV.

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 [8].

The energy and maintenance costs in mixer granulators are higher compared to tumble granulators, except for continuous high-intensity systems, mixers are not viable for high-production

applications if significant growth is required [8]. 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. Unlike tumble and fluid bed granulators, mixer granulators have a wide range of equipment available. These can be arbitrarily divided into high and low shear rate mixers, although there is some overlap in shear rates, the growth mechanisms of granules in mixer granulators are also influenced by the rheology of the wet mass, in addition to shear rates [8].

Figure 1
The Schugi Flexomix® Vertical High-shear Continuous Granulator

High-speed mixers are the most prominent type of mixer in the category of mixer granulators and are divided into high-speed batch mixers and continuous shaft mixers. The latter have blades or pins that rotate at high speed around a central axis. Examples of this type of mixer include the horizontal spike or pin mixers and the vertical Schugi® mixer. These mixers function at a high rate of speed, with a range of 200 to 3,500 rpm, and can produce granules from 0.5 to 1.5 mm in just seconds, allowing for intimate mixing of a pulverized liquid binder and a cohesive, fine feed powder. Nonetheless, due to the limited available time for product densification or growth, the resulting granulated product is usually characterized by irregular, fine, and fluffy particles, with low apparent density. Schugi® and pin mixers can reach capacities of up to 200 tons/h with power requirements of up to 200 kW. Pin mixers typically have capacities of 10 to 20 tons/h [8]. An example of this equipment is shown in Figure 1 [8].

In addition, it should be noted that a fluidized bed dryer is used after completing the granulation operations to fulfill its function. The main difference between the types of fluidized beds lies in the mode of operation, whether it is batch or continuous. Batch fluidized beds can take on different forms. In general, the process chamber contains a perforated plate or sieve at its base and a drying gas outlet at the top, which is often equipped with an internal filter. The drying gas is introduced into the fluidized bed through a plenum chamber located under the perforated plate and exits through the filter. The processed material remains in the chamber throughout the operating cycle [8].

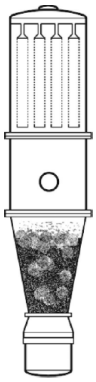


Figure 2
Batch-type Fluid Bed Dryer

Figure 2 [8] shows a schematic representation of a standard batch fluidized bed dryer, which is commonly used in the pharmaceutical and food sectors. The process chamber has a conical shape to generate a flow velocity in the upper section of the chamber compared to the fluidization velocity directly above the perforated plate. This prevents the batch of product contained in the process

chamber from leaving it, allowing for greater freedom in choosing the fluidization velocity compared to a continuous fluidized bed.

Continuous fluid beds offer even more versatility than discontinuous fluid beds, with the main distinction lying in the pattern of solid flow within the dryer. In a continuous fluid bed, there is an entry for wet granular materials that need to be dried and an outlet for the already dried material. If the wet material is immediately fluidizable, it can be directly introduced to the plate and transported through the bed in a plug-flow pattern, which allows for better control of temperature and residence time. If the wet granular material is too sticky or cohesive due to surface moisture and needs to be dried before fluidization, a posterior mixing fluid bed can be used to handle it [8].

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 [8]. Figure 3 illustrates an example of a plug-flow fluid bed.

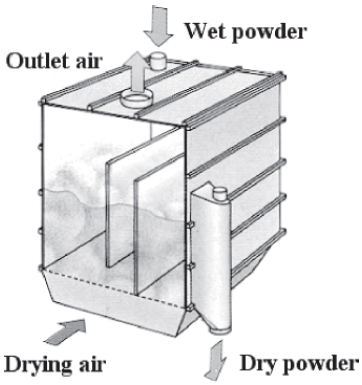


Figure 3
Continuous Plug-flow Fluid Bed

The continuous plug flow fluidized beds, whether fixed or vibrating, can achieve significant benefits by using gill-type fluidized bed plates that can control powder movement along the plate and around curves created by deflectors. Proper utilization of these means can enable the optimization of fluidization velocity, powder residence time, and bed layer height. When fluidized bed technology is applied to drying granular products, offers substantial benefits compared to other drying methods. However, design variables such as fluidization velocity, and residence time required for drying to the specified residual moisture content, and critical moisture content for fluidization must be established through pilot or experimental testing before design implementation. It is feasible to design reliable and highly integrated fluidized bed systems, both discontinuous and continuous, but only through a combination of such pilot testing and industrial experience [8].

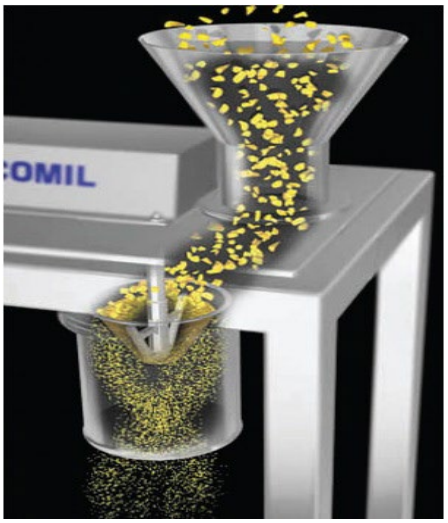


Figure 4
Illustration of Co-mill Overdriven

The cone mill 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. Some advantages of using cone mills are their high efficiency, low heat generation, low dust and noise levels, flexibility, and ease of cleaning and maintenance [9]. A diagram of the overdriven co-milling mill is shown in Figure 4 [10].

Continuous Processes

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 [11].

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. All members of the organization should participate in this process, and the message should be conveyed that continuous improvement is not an isolated program but a series of related programs and projects working together. Additionally, project team formation is essential for studying and making improvement recommendations, which promotes the multifunctional nature of change and the participation of people from different levels and functions in the organization, sending an important message about the systemic nature of change [12].

DMADV Methodology

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. With a structured design approach, the team can achieve streamlined development processes, a shorter time to market, and designs that can be easily implemented [13].

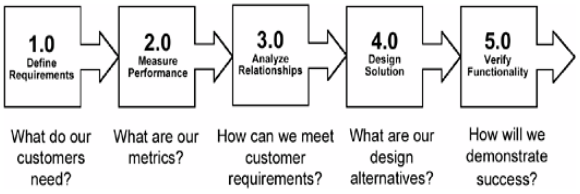


Figure 5
DMADV Flow and Associated Questions

As shown in Figure 5 [13], during the Define phase, emphasis is placed on understanding customer needs and desires, with particular attention to the voice of the customer. In the Measure phase, the focus is on establishing project parameters and developing truly relevant activities. In the Analyze phase, various initial design alternatives are generated. Subsequently, in the Design phase, an approach is chosen from the high-level design alternatives identified in the Analyze phase, and an initial implementation plan is developed. Finally, in the Verify phase, the team verifies that the design meets the requirements [13].

METHODOLOGY

A Six Sigma methodology with a DMADV approach was established in order to achieve the research objectives through a systematic and phased methodology. Since the first research objective is to establish, through the Define Phase, a CTQ (Critical-to-Quality) tree diagram will be developed to determine critical parameters that need to be controlled within the operational units.

Secondly, a measurement process will be carried out, which requires precise, verifiable, and traceable data since decisions are based on the collected data. To achieve this, a data collection plan was established by gathering information from previous studies and reports related to the manufacturing of salbutamol tablets and pharmaceutical industry processes. As a result, a measurement plan and a Measurement System

Analysis (MSA) were generated using the Minitab software. Subsequently, once the critical parameters have been established, a Pareto Chart will be developed in order to measure these parameters.

Furthermore, it is important to understand that when the formulation and manufacturing processes of a pharmaceutical product are optimized through a systematic approach, the scaling and validation of the processes can be highly efficient due to the robustness of the formulation and manufacturing process. The choice of design will depend on the experimental objectives. In this case, the most suitable design type is the Response Surface Method (RSM), which utilizes the specific analysis technique of Comparison of ''Two Processes''.

Subsequently, the Design Phase will be executed to optimize all critical parameters of the continuous line and continue testing and controlling all factors simultaneously. Design of experiments (DOE) and statistical analysis have been widely applied in the development of formulations. The use of DOE will allow for the systematic and timely evaluation of all formulation factors to optimize formulation and manufacturing processes. This explains why the experiment is designed in a way that allows for the estimation of interaction and even quadratic effects, providing insight into the (local) shape of the response surface under investigation.

To achieve this, an extensive observation and analysis will be conducted initially to examine how critical parameters may vary between batch and continuous processes. To determine the similarity or dissimilarity between the two processes, two important assumptions must be made. The first assumption is that data from both processes will follow a normal distribution, while the second assumption is that the standard deviation is unknown.

Finally, the Verification Phase will be carried out to establish the desired control with the critical parameters of the processes for each operational unit. To achieve the desired control with the critical parameters of the processes for each operational unit, X-Bar control chart method will be employed. The data to be used on this chart, including the LCL (lower control limit) and UCL (upper control limit) will be obtained from the Pareto Chart, and the Design of Experiment, after the analysis of the data have been occur by the software program.

RESULTS AND DISCUSSION

The CTQ (Critical to Quality) tree diagram determined the parameters that affect the operating units in the Salbutamol tablet manufacturing process. Since simulation is a powerful tool for understanding the behavior of complex systems and Ishikawa diagrams are an excellent way to visualize results, Minitab software simulation enabled us to observe how different factors interact and affect each other, allowing us to identify possible solutions and strategies. By using an Ishikawa diagram (Figure 6), we can easily interpret the results of our simulations in terms of cause-and-effect relationships in our continuous salbutamol tablet production line.

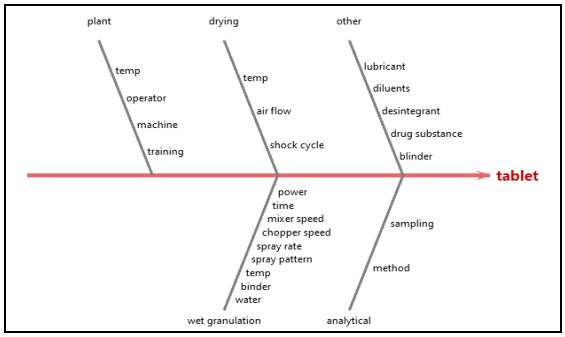


Figure 6
Ishikawa Diagram: Cause-and-Effect Relationship of Experimental Parameter Manipulation

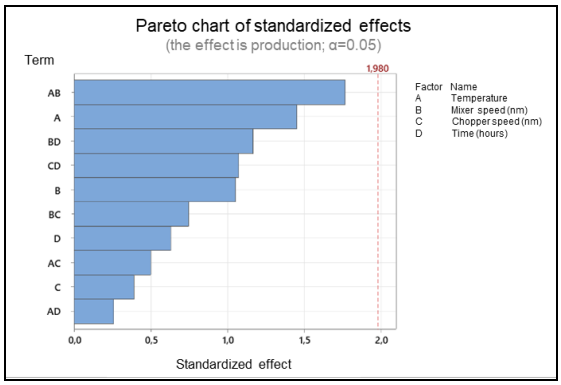


Figure 7
Pareto Chart of Standardized Effects

The result 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. (See Figure 7). Manipulation of this data is significant to model and simulate the behavior of process components and variables, allowing the analysis of their impact on the final product quality and process efficiency.

Table 1
Data considered in Experimental Manipulation

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

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. 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 after and below (Figures 8 and 9) show surface graphs that illustrate how temperature, mixer speed, and chopper speed significantly impact continuous production, as seen at different time points.

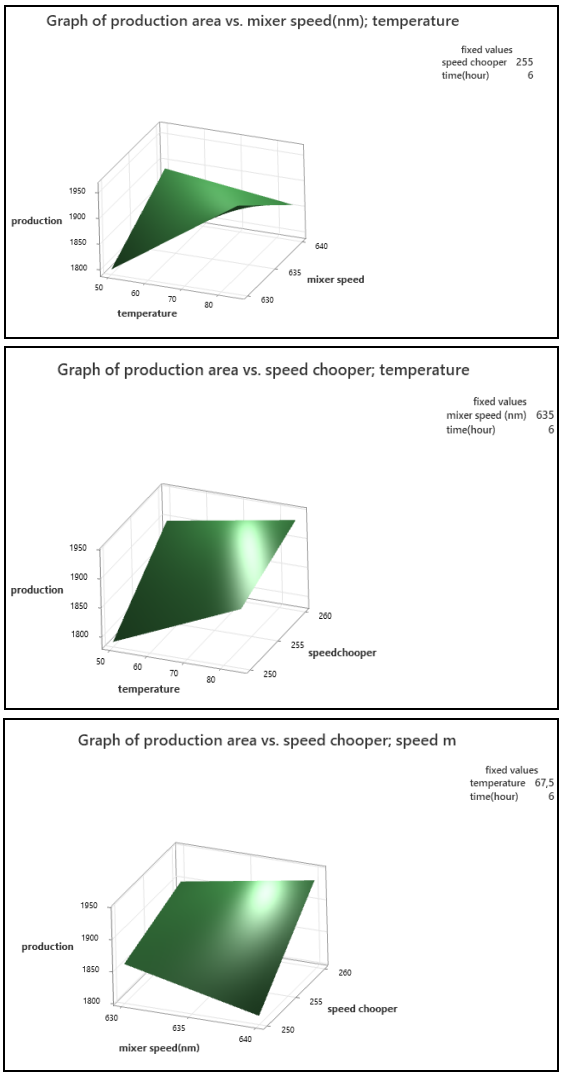
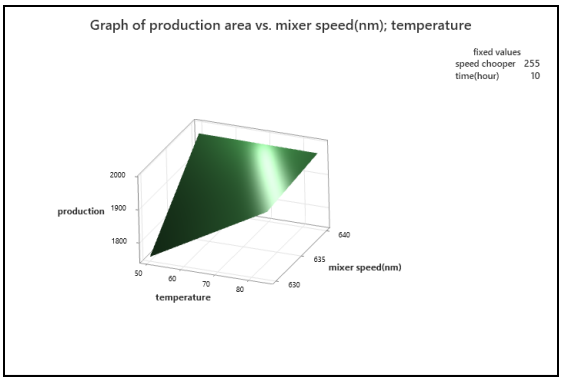
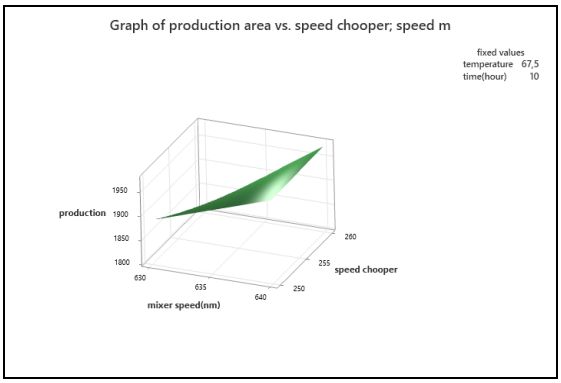


Figure 8
Graphical Representation of RSM at Minimum Time

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 10, 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.





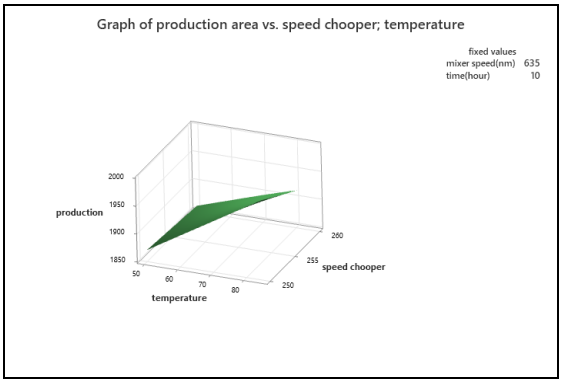


Figure 9
Graphical Representation of RSM at Maximum Time

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 continuous line by the wet granulation method, ensuring high-quality of the final product and efficient production in the process (Figure 11).

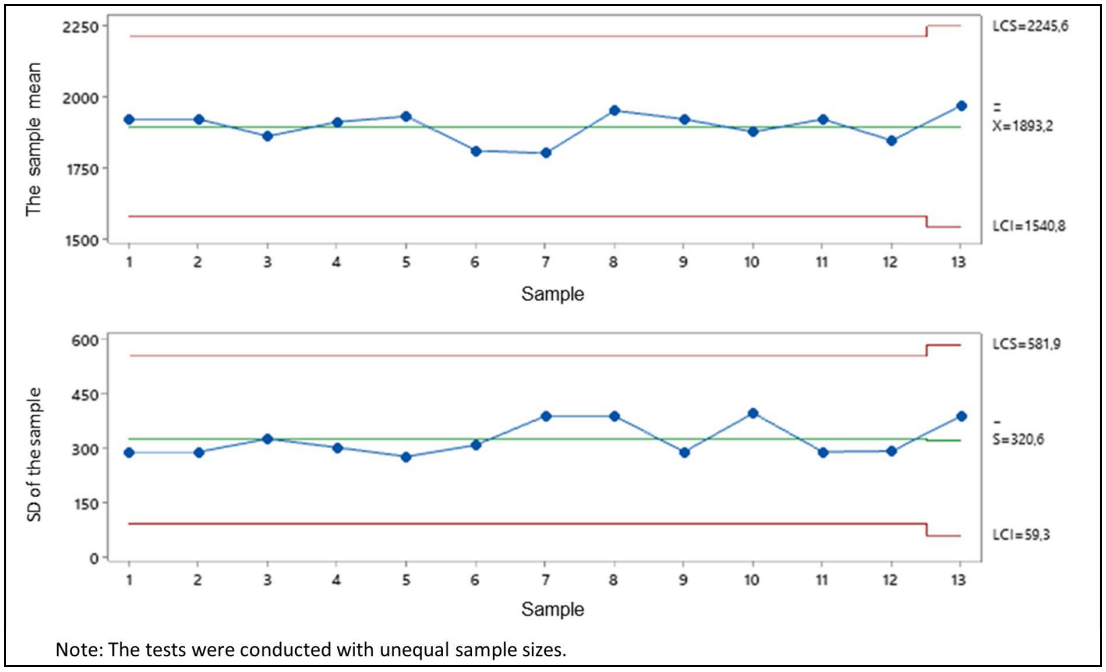


Figure 10
Control Charts (XBar-S Graph of Production)

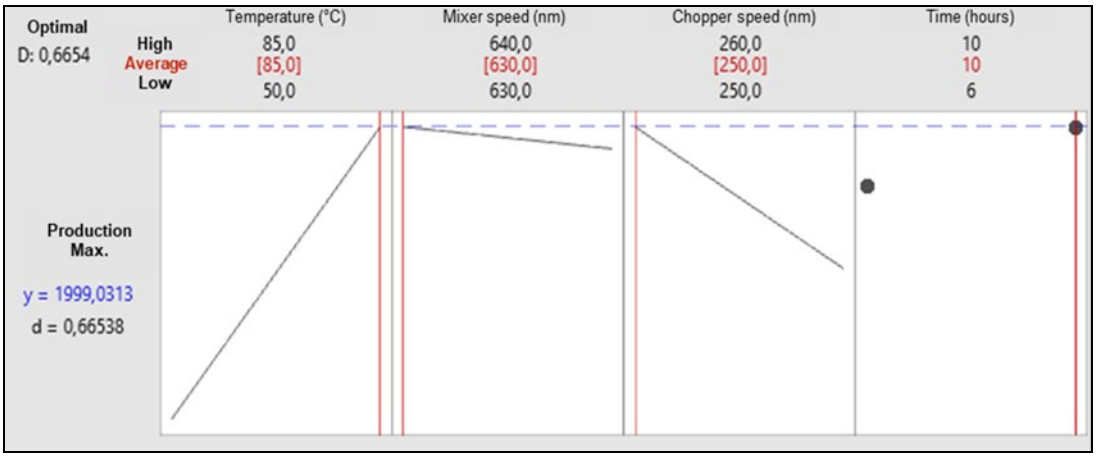


Figure 11
Optimal Data for Maximum Production

CONCLUSION

After conducting the study systematically following the processes established by the DMADV methodology, it was found that the temperature conditions of 85°C, mixer speeds of 630 nm, chopper speed of 250 nm, and a time of 10 hours are the most optimal for the continuous line production of salbutamol tablets by the wet granulation method. However, it is important to consider that although the X-bar chart may indicate that the process is under statistical control, there may still be hidden or undetected problems in the process, and the optimal parameters may vary depending on the specifications and requirements of the formulation, the equipment used, and the production environment conditions. Therefore, it is necessary to perform constant monitoring and adjust the parameters as needed in actual production.

On the other hand, it is important to highlight that one of the major limitations of this project was that, since it is related to the pharmaceutical industry, any reform or implementation of methods related to the product formula could not be considered. Therefore, the project was focused solely on the manipulation of the production process. Even so, results were obtained that optimized production times in a continuous process.

The design of a continuous process for the Salbutamol tablet production plant is a significant contribution to the pharmaceutical industry. It not only allows for improved production times but also reduces losses due to imperfections and hiring costs. Moreover, it provides a social benefit to all those who make use of this pharmaceutical and represents a noteworthy contribution to researchers or professionals in the field who consider implementing a continuous manufacturing process using DMADV. Therefore, researchers are encouraged to follow the process and consider implementing this design in a production plant to measure and compare its results.

REFERENCES

[1] M. Billups & R. Singh, "Systematic Framework for Implementation of Material Traceability into Continuous Pharmaceutical Tablet Manufacturing Process," in *Journal of Pharmaceutical Innovation*, 2020, vol. 15, no. 1, pp. 51–65. DOI: 10.1007/s12247-018-9362-9.

[2] J. Smith. (2017). "The Pros & Cons of Batch Production - Global Electronic Services," in *Global Electronic Services* [Online]. Available: https://blog.gesrepair.com/2017/06/03/the-pros-cons-of-batch-production/. [Accessed: Mar. 9, 2023].

[3] J. Kochling. (2019). *Q&A session with Jianmei Kochling. Homepage - Oxford Global* [Online]. Available: https://www.oxfordglobal.co.uk/wp-content/uploads/2019/10/Jianmei-Kochling-QA.pdf. [Accessed: Mar. 9, 2023].

[4] N. D. Olivera, L. Pardo, G. Monteverde, F. Saralegui, V. Kanopa & G. Giachetto, "Reacciones adversas por salbutamol en pacientes asmáticos: reflexiones acerca del uso en las exacerbaciones," in *Archivos de pediatría del Uruguay*, 2021, vol. 92, no. 2. Available:

http://www.scielo.edu.uy/scielo.php?script=sci_arttext&pid=S1688-12492021000301305.

[5] WHO. (2022). *Asthma* [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/asthma. [Accessed: Mar. 7, 2023].

[6] Medicina y Salud Pública. (2020). *Perfil epidemiológico del asma en Puerto Rico. Medicina y Salud Pública* [Online] Available: https://medicinaysaludpublica.com/noticias/alergologia/perfil-epidemiologico-del-asma-en-puerto-rico/5682. [Accessed: Mar. 7, 2023[.

[7] M. S. Borawake, "Quality Improvement for LED Lights using Six Sigma," *International Research Journal of Engineering and Technology (IRJET)*, 2019, vol. 6, no. 12, pp. 2720-2724. Available: https://www.irjet.net/archives/V6/i12/IRJET-V6I12404.pdf.

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

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

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

[11] D. J. Am Ende & M. T. Am Ende, "Chemical Engineering in the Pharmaceutical Industry," in *Chemical Engineering in the Pharmaceutical Industry*, 2019, pp. 1–17. DOI:10.1002/9781119600800.ch51.

[12] D. Cleland, *Project Management: Strategic Design and Implementation*, 5th ed. The McGraw-Hill Companies, Inc., 2007.

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