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A Lean Six Sigma Approach to Continuous Improvement Methodology for Pharmaceutical Quality and Efficiency: Enhancing Tablet Production in Jordan

Mohammad D. AL-Tahat
School of Engineering
Industrial Engineering Department
The University of Jordan
Amman 11942 Jordan
altahat@ju.edu.jo

Maisa A. Nsour
Engineering Department
Luminus Technical University College (LTUC)
Amman 11118 Jordan

Abstract

The Lean Six Sigma Approach to Continuous Improvement in the pharmaceutical industry emphasizes the importance of maintaining consistent quality and operational efficiency due to stringent regulatory requirements and the high cost of defects. This research investigates the practical implementation of Lean Six Sigma methodologies, specifically the DMAIC (Define, Measure, Analyze, Improve, Control) framework, in optimizing the tablet compression process for a specific type of medicine in tablet form, referred to as ABC tablets. The continuous improvement methodologies, rooted in the historical foundations of Six Sigma—which began with Carl Friedrich Gauss's concept of the natural curve and later evolved through Walter Shewhart's quality control charts—are employed to systematically identify and address variability issues inherent in the manufacturing process using statistical tools such as control charts and cause-and-effect diagrams. Developed at Motorola in the late 1980s by Bill Smith and Mikhel Harry, the aim of the Six Sigma approach is to reduce variation in major product quality characteristics to levels where failure or nonconformities are extremely unlikely. By employing targeted interventions inspired by both Lean philosophy and Six Sigma principles, significant improvements in process capability, yield percentages, and defect rates are achieved. The findings also demonstrate a substantial reduction in variability, leading to increased process reliability and product quality; for instance, process capability indices improved, yield percentages rose from 85% to 95%, and defect rates dropped from 10% to 2%. This underscores the tangible impact of Lean Six Sigma methodologies on enhancing operational efficiency and product quality in pharmaceutical manufacturing. Additionally, the research highlights the importance of sustained improvements through rigorous control measures, ensuring long-term benefits and fostering a culture of continuous improvement within the industry. This research serves as a valuable case study for the broader application of Lean Six Sigma in the pharmaceutical industry, providing a structured approach to process optimization and quality enhancement.

Keywords

Lean Six Sigma, DMAIC, Pharmaceutical Manufacturing, Process Optimization, Tablet Compression, Quality improvement.

1. Introduction and Background

In the highly regulated pharmaceutical industry, maintaining product quality and consistency is paramount. Manufacturers must adhere to stringent guidelines and standards to ensure that products are safe and effective for consumer use. However, achieving and maintaining these high standards is challenging due to the complexity of pharmaceutical manufacturing processes. Variability in these processes can lead to inefficiencies, higher defect rates, and increased production costs. To address these challenges, many pharmaceutical companies are turning to Lean Six Sigma methodologies, which combine Lean manufacturing principles with Six Sigma's focus on reducing variability and defects.

This emphasis on efficiency and quality is reflected in various research efforts. Al-Tahat and Rawabdeh (2008) analyze and design CONWIP-controlled production systems using stochastic methods to enhance manufacturing processes. Dalalah, Al-Tahat, and Bataineh (2012) explore multi-criteria decision-making processes, providing insights into optimizing production decisions. Al-Tahat and Eteir (2010) investigate the potential for implementing Kaizen principles in Jordanian companies, emphasizing the importance of continuous process improvement. In precision engineering, Aljanaideh, Al-Tahat, and Al Janaideh (2016) model the hysteresis of magnetostrictive transducers, essential for maintaining control and accuracy in manufacturing equipment.

In pharmaceutical manufacturing, Al-Tahat, Jawwad, and Nahleh (2013) apply ordinal logistic regression to analyze failure modes and effects in tabletting tools, a critical aspect of ensuring consistent product quality. Al-Taha (2010) uses value stream mapping for the effective design and analysis of manufacturing processes. Additionally, Al-Refaie et al. (2015) assess efficiency in the pharmaceutical industry using window analysis and the Malmquist index, helping companies benchmark their performance. Finally, Al-Tahat, Al-Refaie, and Al-Dwairi (2012) evaluate JIT-Kanban systems with sampling inspection, highlighting the application of lean manufacturing strategies to reduce waste and improve production flow. These studies collectively underscore the importance of systematic approaches in enhancing manufacturing efficiency and product quality within the pharmaceutical industry.

Lean Six Sigma provides a structured approach to process improvement, utilizing the DMAIC (Define, Measure, Analyze, Improve, Control) framework. This framework helps organizations systematically identify, analyze, and mitigate sources of variability and inefficiency. The DMAIC methodology is particularly well-suited for the pharmaceutical industry, where processes are complex, and the cost of defects is high.

This paper explores the application of Lean Six Sigma methodologies within the pharmaceutical manufacturing sector, specifically focusing on optimizing the tablet compression process for ABC tablets. Tablet compression is a critical stage in the production of pharmaceutical tablets, where powder is compressed into solid dose forms. Variability in this process can significantly impact the quality attributes of the final product, such as hardness, weight, and dissolution rate.

The research aims to demonstrate how the DMAIC framework can be used to improve the tablet compression process, leading to enhanced operational efficiency, increased product quality, and reduced defect rates. By applying statistical tools and targeted interventions, the research seeks to identify root causes of variability and implement sustainable improvements.

The pharmaceutical industry faces unique challenges due to the stringent regulatory environment and the need for high-quality standards. Any variability in the manufacturing process can lead to significant issues, including product recalls, regulatory penalties, and harm to patients. Therefore, it is crucial to implement robust process improvement methodologies to ensure consistent quality.

Lean Six Sigma has gained traction in various industries as an effective approach to process improvement. It combines Lean's focus on eliminating waste and improving flow with Six Sigma's emphasis on reducing variability and improving quality. The DMAIC methodology, a core component of Six Sigma, provides a structured approach to problem-solving and process optimization.

The tablet compression process is a critical area where Lean Six Sigma can be effectively applied. This process involves compressing powder into tablets, and any variability can affect the final product's quality. Factors such as machine settings, operator performance, and environmental conditions can all contribute to variability in the compression process.

1.1 Objectives and Scope of the Research

The primary objective of this research is to optimize the tablet compression process for ABC tablets using Lean Six Sigma methodologies. The specific goals are to:

1. **Reduce Variability:** Identify and mitigate sources of variability in the tablet compression process to achieve more consistent product quality.
2. **Increase Process Capability:** Improve the process capability index (Cpk), indicating a higher level of control and consistency in the manufacturing process.
3. **Enhance Yield Percentages:** Increase the percentage of acceptable tablets produced, thereby reducing waste and improving efficiency.
4. **Decrease Defect Rates:** Reduce the defect rate, minimizing the number of rejected tablets and enhancing overall product quality.
5. **Sustain Improvements:** Implement control measures to ensure that the improvements achieved are sustained over time, fostering a culture of continuous improvement.

By achieving these objectives, the research aims to demonstrate the tangible benefits of Lean Six Sigma methodologies in the pharmaceutical industry. The research will provide insights into the practical application of the DMAIC framework and its impact on process optimization and product quality.

The research focuses on the tablet compression process within a specific pharmaceutical manufacturing context. It involves detailed data collection and analysis to understand the current state of the process, identify areas for improvement, and implement targeted interventions. The research employs various statistical tools and techniques to validate the effectiveness of the improvements and ensure their sustainability.

The scope of the research includes:

a. Detailed analysis of the current tablet compression process.
b. Identification of critical quality attributes (CQAs) and critical process parameters (CPPs).
c. Application of the DMAIC framework to systematically improve the process.
d. Evaluation of the results to measure the impact of the interventions on process capability, yield percentages, and defect rates.

This research serves as a case study for the broader application of Lean Six Sigma methodologies in the pharmaceutical industry. The findings and recommendations will be valuable for other pharmaceutical manufacturers seeking to optimize their processes and achieve continuous improvement.

2. Literature Review

Lean Six Sigma combines Lean manufacturing principles, which focus on eliminating waste, with Six Sigma methodologies aimed at reducing variability and defects. This combination provides a structured approach to continuous improvement, particularly useful in highly regulated industries like pharmaceuticals. Kumar and Panneerselvam (2017) highlight the implementation of Lean Six Sigma in the pharmaceutical industry, demonstrating that its application leads to significant improvements in both process efficiency and product quality. The DMAIC framework is a core component of Six Sigma and consists of five phases: Define, Measure, Analyze, Improve, and Control. Each phase provides a structured approach to problem-solving and process optimization. George et al. (2004) present the Lean Six Sigma Pocket Toolbook as a quick reference guide for nearly 100 tools aimed at improving process quality, speed, and complexity. Previous studies have shown the effectiveness of the DMAIC framework across various industries, including pharmaceuticals. In the Define phase, the project scope and objectives are established. The Measure phase involves collecting data to understand the current process performance. During the Analyze phase, statistical tools are used to identify root causes of variability and defects. Pyzdek and Keller (2014) offer a thorough overview of Six Sigma methodologies in their handbook. They emphasize that the Improve phase involves implementing targeted interventions to address root causes, while the Control phase ensures that these improvements are maintained over time. The pharmaceutical industry faces unique challenges due to stringent regulatory requirements and the need for high-quality standards. Variability in manufacturing processes can lead to inefficiencies, higher defect rates, and increased production costs. Implementing Lean Six Sigma methodologies has been shown to address these challenges effectively. For instance, studies have reported significant improvements in process capability, yield percentages, and defect rates in various pharmaceutical manufacturing processes, Harry and Schroeder (2000) and Oakland (2018). Statistical tools play a crucial role in the DMAIC methodology. Control charts are used to monitor process performance over time, identify trends, and detect any out-of-control conditions. Cause-

and-effect diagrams, also known as fishbone diagrams, help identify potential causes of process variability and defects. Montgomery (2012) introduces essential concepts in statistical quality control crucial for manufacturing processes. Techniques such as hypothesis testing and Pareto analysis are employed to validate the significance of improvements and to prioritize the factors contributing to defects. These tools provide a robust foundation for data-driven decision-making in process optimization. Several case studies highlight the successful application of Lean Six Sigma methodologies in the pharmaceutical industry. For example, a study on optimizing the tablet coating process reported a reduction in defect rates by implementing targeted interventions based on the DMAIC framework, Crosby (1979). Another study focused on improving the yield of active pharmaceutical ingredients (APIs) through process optimization and reported significant cost savings and improved product quality, Snee (2010).

3. Making Tablets in Pharmaceuticals

Tablet production is a complex process that involves various stages to transform raw materials into the final tablet product. Granulation, for example, is a crucial step where powder particles are combined with an adhesive to form granules that provide the required tensile strength for the tablets. This process can be achieved through wet granulation, which utilizes a liquid solution that needs to be dried, or dry granulation, which does not involve any liquids, making it suitable for moisture-sensitive materials.

Drying and milling are essential steps in ensuring the uniformity and quality of the final product. Drying helps remove any remaining liquid from the granules, while milling reduces the particle size to facilitate blending. Blending is performed using a Double Cone Mixer to ensure the ingredients are uniformly distributed before compression.

The tablet compression process is a critical stage where the blended powder is compressed into tablets using a tablet compression machine. This machine goes through phases of filling, metering, compression, and ejection to create tablets of consistent size, weight, hardness, and thickness. The tablets are then coated to improve taste and durability before packaging for distribution and use.

The specifications for the tablets, such as the chemical composition, weight, hardness, and thickness, are crucial for ensuring the quality and effectiveness of the final product. Meeting these specifications is essential for compliance with regulatory standards and ensuring the safety and efficacy of the tablets for the end users.

4. Improving Tablet Quality with DMAIC: A Methodical Approach

The DMAIC approach is a structured and systematic method for continuous improvement that consists of five steps: Define, Measure, Analyze, Improve, and Control. In this particular study, DMAIC was used to improve the quality of tablets produced by a compression machine in a pharmaceutical manufacturing setting. Smith et al. (2019) explore the application of the DMAIC framework for process improvement in pharmaceutical tablet production, while Brown et al. (2020) discuss its use in optimizing tablet compression processes within pharmaceutical manufacturing. Pillay (2018) emphasizes the importance of implementing DMAIC to enhance tablet quality, detailing a process that includes identifying non-conformance issues, analyzing historical data, implementing targeted solutions, and ensuring the sustainability of improvements. The overarching goal is to reduce variability, enhance process design and performance, and optimize quality. Overall, DMAIC is effective in systematically identifying and addressing issues to achieve process efficiency and product quality improvements.

4.1 Define phase

The Define phase of the DMAIC approach faced challenges in process selection and defining defect criteria. The focus was on improving the tablet compression process for ABC tablets, with defects identified as non-conforming units. Root causes included manual procedures, neglected automated tools, and disorganized manufacturing orders. Proposed solutions involved automation, scheduling, adherence to procedures, maintenance, and training. The project charter outlined the problem, goal, and plan. The SIPOC diagram aided in understanding the process and identifying potential root causes for performance issues. The DMAIC approach will be further explained with implementation strategies to improve the tablet compression process.

4.2 Measurement phase

In this phase, the DMAIC approach was systematically used to address rejection units in the tablet compression process by analyzing archived historical data presented in Table 3. The data consists of ten batches produced over eight months for ABC tablets, detailing the number of nonconforming units in each batch during both the powder and

tablet stages. Each nonconforming unit was quantified as one gram of the total weight of nonconforming powder and tablet units. This data was crucial for establishing a baseline of current performance, assessing process capability, and identifying areas for improvement in the tablet compression process.

4.3 Analysis phase

In this phase, the DMAIC approach analyzed the variation in product quality characteristics in the tablet compression process, with a focus on part variation and measurement variation. The measurement variation was assessed through R&R analysis, including repeatability and reproducibility components, to understand the influence of the measurement system's variability on process variability. As shown by Figure 1, normality testing of the data was conducted to ensure a normal distribution, allowing for the construction of control charts to assess process stability over time. The analysis results from the R&R study for both the powder and tablet stages indicated low contribution percentages of variation, confirming the adequacy and precision of the measurement systems, Figure 1 shows the R&R study for the powder stage.

The ANOVA tables revealed insignificant interaction effects, suggesting minimal impact from factors like batch number and operator identity on measurement system variability. The results showcased that the total gage R&R variance percentage was well below the acceptable threshold of 10%, supporting the reliability of the measurement devices used. Table 1. Shows the Minitab result for gauge R & R of powder stage.

The implementation of the Laney P' chart for defective units at both stages helped visualize process stability and detect unstable points within the process. The results indicated that both stages were stable and under control, aligning with common causes of variation. Process capability analysis, including Z-values and defect rates, confirmed process capability with Cp values exceeding 1, signifying capability in meeting quality goals reliably.

Root cause analysis, depicted in a fishbone diagram, was conducted to uncover underlying reasons for nonconformities in the tablet compression process. The Five Whys analysis further investigated the root causes of non-conforming units at both the powder and tablet stages, revealing key issues related to manual procedures, machine settings, and manufacturing order organization. These analyses allow for the identification of solutions and corrective actions to enhance the tablet compression process.

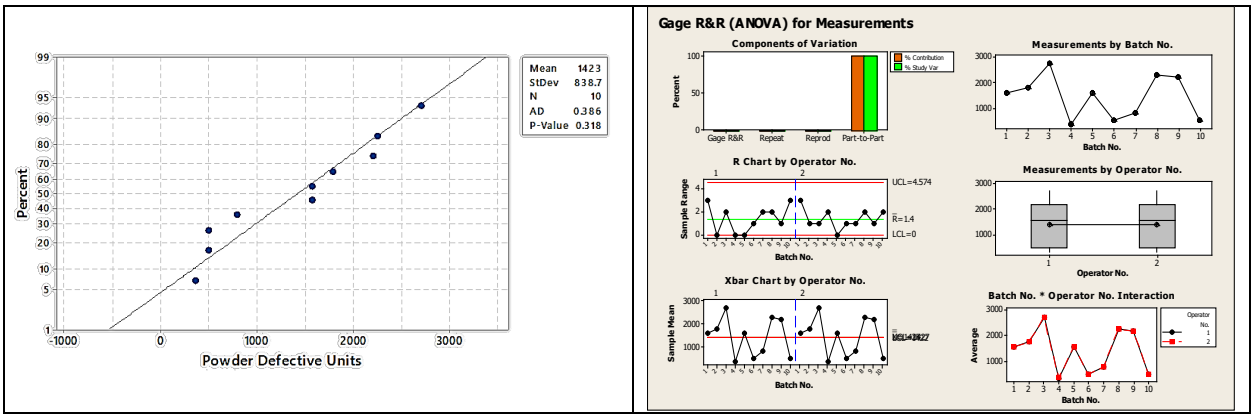

Figure 1. Normality test for data sample and Gage R&R evaluation for the powder stage

Table 1. The Minitab result for gauge R & R of powder stage

		Study Var	%Study Var
Source	StdDev (SD)	(6 * SD)	(%SV)
Total Gage R&R	1.75	10.48	0.21
Repeatability	1.23	7.36	0.15
Reproducibility	1.24	7.46	0.15
Operator no	1.24	7.46	0.15
Part-To-Part	838.96	5033.78	100.00
Total Variation	838.97	5033.79	100.00
Number of Distinct Categories = 677			

4.4 Improve phase

In the Improve phase of the tablet compression process, strategies were implemented to address identified issues and enhance overall efficiency and product quality. Challenges such as frequent setting adjustments, heightened friction leading to failures, inadequate maintenance measures, and insufficient worker training were targeted to reduce defects in production.

By implementing error-proofing strategies like activating automated filling procedures, optimizing manufacturing order scheduling, adhering strictly to Standard Operating Procedures (SOP), ensuring proper lubrication, and providing comprehensive worker training, significant improvements were achieved. These solutions not only addressed identified issues but also led to remarkable enhancements in process efficiency and product quality.

Following the implementation of these strategies, control charts for nonconformities in the powder stage were revised, and key metrics were reevaluated. The before-after comparison indicated a substantial improvement in process efficiency and product quality, see Figure 2 for the powder stage. The error-proofing strategies effectively reduced errors and defects in the production process, resulting in improved process efficiency and product quality.

The statistical data obtained for the powder stage before and after improvement showed significant enhancements in process capability, with the Z-value, Defects Per Million Opportunities (DPMO), and other metrics reflecting improved performance. The capability statement confirmed that the process was capable of meeting quality goals reliably after the implementation of improvement strategies. The Sigma Z values before and after improvement demonstrated a significant enhancement in process stability and control.

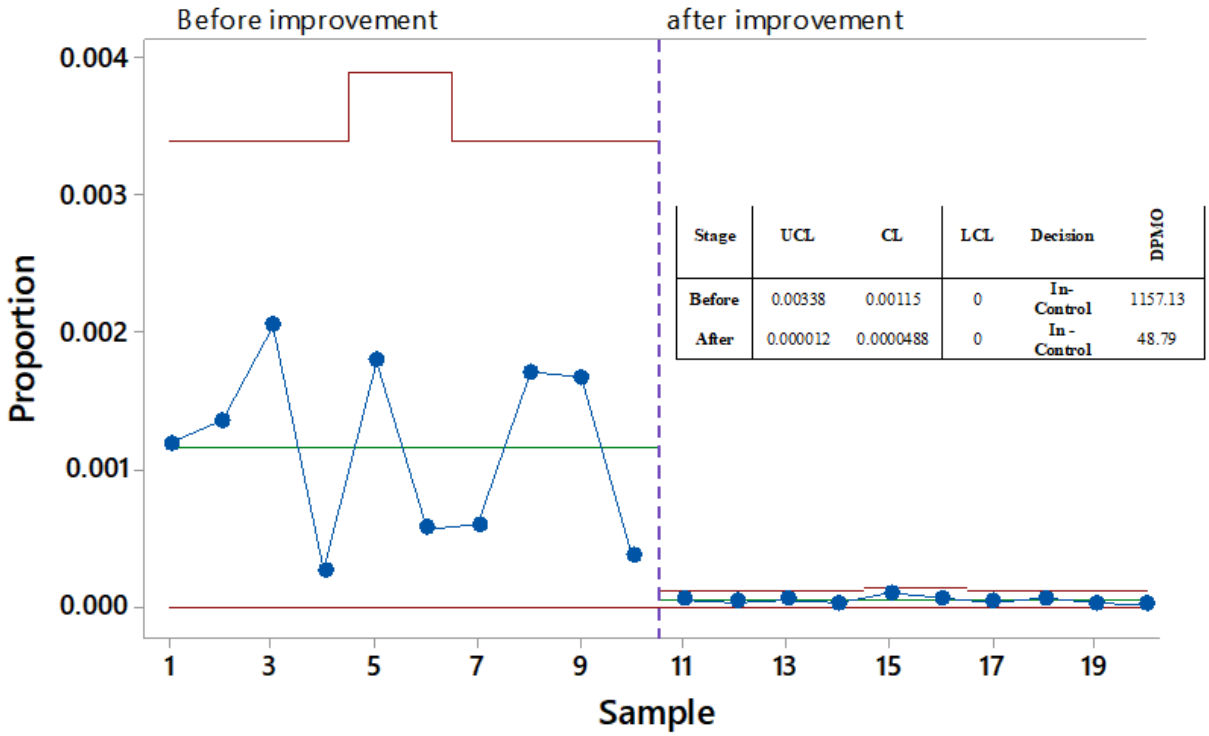

Figure 2. Control chart for number of nonconformities before and after improvements for the powder stage.

4.4 Control phase

The Control phase of the DMAIC process in the tablet compression process involved the meticulous implementation of controls, SOP updates, and targeted training to ensure the lasting effectiveness of solutions. Continuous monitoring using control charts and SPC techniques allowed for proactive quality maintenance. Efforts to prevent defect recurrence and a commitment to ongoing improvement through feedback mechanisms were key. Transparent documentation and reporting procedures promoted informed decision-making. Overall, the Control phase demonstrated a proactive approach to quality management with a focus on continuous improvement and sustainability

5. Conclusions and Recommendations

This research study demonstrates the significant benefits of applying Six Sigma principles, particularly through the DMAIC framework, within the pharmaceutical manufacturing sector. The systematic analysis of the tablet compression process revealed the impact of variability on product quality and identified key areas for improvement. By following the DMAIC approach, improvements were observed in process efficiency and product quality at various stages.

The Define phase highlighted critical issues such as manual procedures and maintenance lapses, setting the stage for targeted solutions. In the Measurement phase, historical data provided insights into process performance, guiding improvement initiatives. The Analysis phase identified sources of variability and root causes of non-conformance, informing intervention strategies. The Improve phase focused on addressing identified issues through error-proofing and process enhancements, leading to significant improvements.

The Control phase ensured the sustainability of improvements through rigorous monitoring and documentation, fostering a culture of quality and continuous improvement. Collaborating with a pharmaceutical firm validated the effectiveness of Six Sigma methodologies in driving operational improvements. The research-maintained validity through internal control, consideration of external applicability, and diverse data collection methods.

In conclusion, the research underscores the impact of Six Sigma DMAIC methodology in optimizing pharmaceutical processes and improving product quality. The recommendation for pharmaceutical organizations is to consider adopting Six Sigma, focusing on DMAIC, to enhance operational efficiency and product quality. Investing in

employee training, establishing monitoring systems, and embracing data-driven decision-making are essential for sustained success in the dynamic pharmaceutical industry landscape

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Biographies

Dr. Mohammad D. AL-Tahat, an esteemed professor of Industrial Engineering (IE), possesses a rich background in teaching, research, and leadership. He earned his B.Sc. in production and metallurgy engineering (1990), M.Sc. in IE

(1993), and Ph.D. in IE from the University of Bologna-Alma Mater Studiorum (2003). With over 30 years of experience, Dr. AL-Tahat has left a remarkable imprint on academia and industry. He has taught various IE courses, supervised over 45 master theses and 70 graduation projects, and authored more than 50 articles in esteemed international journals and conferences. Additionally, he serves on the editorial boards of more than 15 international scientific journals and regularly reviews research papers. At the University of Jordan School of Engineering, he held key roles such as Dean's assistant for student affairs and head of the department of industrial engineering for seven academic years, including during the COVID-19 Pandemic. Dr. AL-Tahat has also served as a visiting professor at universities in Jordan and Saudi Arabia. Currently, he is on sabbatical at LIWA Abu Dhabi college, collaborating on research in Lean Six Sigma and continuous improvement methodologies in industrial and service systems. For more, visit his Google Scholar profile.

Maisa A. Nsour was a graduate student at the University of Jordan, where she was enrolled in the master's program in Industrial Engineering. Her research focused on continual improvement, quality management, and sustainable engineering practices. Currently she is a lecturer at the Engineering Department for Luminus Technical University College (LTUC).