INDIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ORIGINAL ARTICLE

Operational Excellence: A Model Pathway to Improve Yield and Productivity of the Pharmaceutical Tablet Manufacturing Process

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OPEN ACCESS

Received: 27/10/2025
Accepted: 14/11/2025
Published: 15/12/2025

Citation: Gaidhani VV, Chavan DP, Sonwane PN, Gadakh PM, Patil SV, Shirsath S (2025) Operational Excellence: A Model Pathway to Improve Yield and Productivity of the Pharmaceutical Tablet Manufacturing Process. Indian Journal of Science and Technology 18(46): 3658-3669. https://doi.org/10.17485/IJST/v18i46.1758

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Funding: None

Competing Interests: None

Published By Indian Society for Education and Environment (iSee)

ISSN
Print: 0974-6846
Electronic: 0974-5645

Abstract

Background: Operational Excellence (OE) is a management principle widely adopted in the pharmaceutical industry to optimize manufacturing processes and to improve yield and productivity up to 20%. OE was based upon a few principles, tools, and techniques such as Lean, Six Sigma, JIT, FIFO, FEFO, statistical analysis, etc. Lean and Six Sigma (LSS) will reduce production defects by **30–50%**, shorten batch release time by **25–40%** in the pharmaceutical manufacturing company. **Objective:** This review aims to correlate the key process parameters of manufacturing with the application of OE tools to improve Overall Equipment Effectiveness (OEE) by **15–35%** and reduce process variability (σ) by **40–60%**. Also, provide a framework to the industry to implement OE with statistical tools. **Method:** In this review, DMAIC methodology is used to demonstrate the process flow of change and improvement. OE is a continuous process that ensures quality compliance, improved yields, and robust processes. OE highly impacts the 4 M's, i.e., Material, Method, Money, and Manpower. An example of a bilayer tablet has been considered for study purposes. However, this technique is widely applicable to all types of dosage forms. **Findings:** OE is gaining larger importance in the pharmaceutical industry as manufacturers focus on issues like cost-cutting **(by15%),** quality improvement, and customer satisfaction **(20-30%)**. This study indicates that understanding the manufacturing process from the perspective of OE is vital before initiating any change in the process, which will directly affect yield and the overall industrial environment. **Novelty:** This review focuses on the application and implementation of various OE tools at the industrial and/or commercial level without compromising with the cGMP criterion, which are defined by the regulatory authorities. This will allow the manufacturer to focus on quality improvement in crucial products in terms of quality, large commercial volume, and market value.

Keywords: Operational Excellence (OE); Lean Six Sigma (LSS); Bilayer Tablet (BT); Lean Manufacturing (LM); Pharmaceutical Manufacturing

1 Introduction

Lean Six Sigma (LSS) technology is gaining importance in the pharmaceutical industy as it allows industries to implement new methodologies to develop a solid, robust process of manufacturing [1], [2].

Bilayer oral solid dosage forms, i.e., bilayer tablets (BT), is an emerging field of research and are highly demanded products, as fixed-dose combination of drugs can rely on bilayer tableting technologies. [3] It allows us to formulate two or more incompatible dosage forms together. This bilayer tableting technology plays an immense role in achieving therapeutic effect for a fixed dose combination and maintains the product at its highest quality attributes [4]. Operation Excellence allows industries to run projects like yellow belt, green belt, and black belt to achieve high yield and productivity. This type of project is executed at the industry level to optimize the commercial scale finish goods in terms of yield and productivity.

1.1 Operational Excellence

OE provides a system for process improvement. It is a management principle that provides tools to improve product quality, improve product yield, improve process flow and compliance, inventory management, and cost reduction [5], [6], [7]. Let's further understand in detail about OE tools.

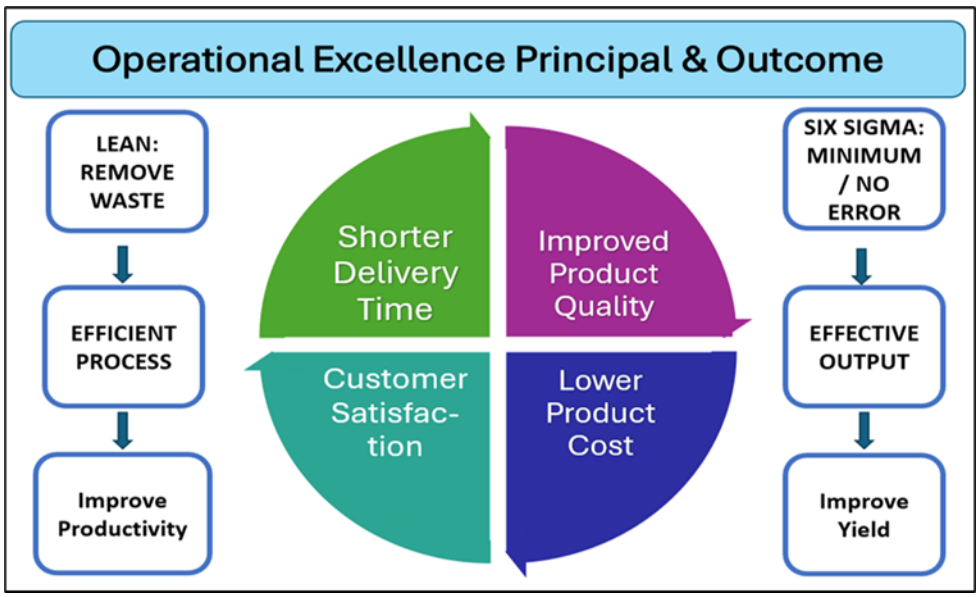

Fig 1. Basic Principle of Operational Excellence

1.1.1. Lean

Lean is a process that delivers a product or service as per the customer's requirement at a price that reflects only the value that customer is willing to pay, i.e., faster response and flexible Process [8], [9]. This is achieved by eliminating waste from any activity and getting more output from fewer resources. The result will be the availability of additional capacity. The cost of the activity will be reduced. Lean implementation will ensure the employee's well-being by doing organized and efficient work, resulting in a reduced stress level [10]. What prevents us from achieving a lean environment can be classified into 8 types of **waste** (for which the customer is not willing to pay), namely Transportation, Inventory, Motion, Waiting, Overproduction, Over-Processing, and Intellectual Waste. [11].

1.1.2. Six Sigma

Sigma is the standard deviation (s), which is a very useful tool in expressing the quality of a process. The smaller the deviation from the standard (average of the process data points), the better the process control [12]. The objective of using this tool is to measure the capability of a process and where the focus is needed to improve the standard deviation and ultimately the quality of a product [13].

Table 1. Levels of Sigma

Sigma Level	Defects per Million (DPM)	Yield (%)
6	3.4	99.999966%
5	230	99.977%
4	6210	99.38%
3	66800	99.32%
2	308000	69.15%
1	690000	30.85%

1.1.3. Productivity

Productivity is defined as the physical relationship between the quantity produced (output) and the number of resources used during production (input)" i.e., at the same cost in terms of land, materials, machines, time, or labor, etc.[14]. Productivity is the ratio between output and input. It is defined by the relationship between the gained output and one or all associated inputs.

1.1.4. OE Technique and tools

OE techniques and tools are based on various management principles[15]. Lean techniques are Just in Time (JIT), Quality Circles, One Piece Flow (OPF), Kaizen, Benchmarking, Quality Function Deployment (QFD), and Failure Modes and Effect Analysis (FMEA). Lean tools used in OE are Kanban, Poka-Yoke, Value Process/Stream Mapping (VSM), Spaghetti Diagram (SD), 5S/6S, Tack Time, and Ishikawa. Six Sigma principles are based upon these techniques, such as Statistical Process Control (SPC), Taguchi Method, Benchmarking, Quality Function Deployment (QFD), Failure Modes, and Effect Analysis (FMEA), and Design of Experiment (DOE). Implementation of the Six Sigma principle is done with the help of tools like Poka-Yoke, Ishikawa, Control Charts, Regression Analysis (RA), Measure Capability, and Correlation Studies.

1.2 Bilayer Tablet manufacturing process and parameters

The example of a bilayer tablet is taken as it is gaining more choice of dosage form among the pharmaceutical industry. It has a very crucial manufacturing process. In the bilayer tablets two or more APIs are manufactured differently at the fabrication stage and compressed layer by layer. For example, one layer of tablet is fabricated by blending raw material, and the other is fabricated by wet granulation technology. These blends are compressed at a Double Rotatory (DR) tablet press machine. Here, the ratio of layers is an important parameter, both in tablet and in batch. Hence, cGMP In-process parameters in BT manufacturing need to be monitored[16],[3]. The study considered first two stages of manufacturing, i.e. granulation and compression, to understand the process parameters. Table 2 has defined in-process test and acceptance criteria at the granulation and compression stage as per cGMP regulations, which importance is discussed in the study.

1.3 Research Contributions

As the relationship between material properties and process parameters determines the quality of the finished product, the pharmaceutical industry is looking for continuous processing to enhance production efficiency and product quality[17]. This study summarizes the relationship between the drug product properties and process parameters, which leads to variation in the final yield.

1.4 Research Gaps

Literature surveys show that OE techniques have been followed by many industries, including pharmaceutical and healthcare for decades, but in very discrete patterns. A complete project dedicated to overall production and/or individual dosage form manufacturing lacks written literature. In the pharmaceutical industry, many issues faced by management are maintaining supply-chain, manufacturing capacity and throughput short fall, regulatory compliance, product cost and overall financial management, maintaining quality culture at all levels, technology transfer and scalability, data integrity and many more. With the implementation of OE principles and techniques, such issues can be addressed at a deeper level.

1.5 Research Questions

This study will help to address the following questions

Table 2. In-Process Test and Acceptance Criteria at the Granulation and Compression Stage According to cGMP

Granulation		
Parameter	**Production**	**IPQA**
1. Sieve Integrity	Before Batch Start and at the Batch End	Before Batch Start
2. Roll Compactor	Every 30 min	NA
3. FBD Bag and FBD Screen Integrity	Before Batch Start and at the Batch End	Before Batch Start and at the Batch End
4. LOD	At least Once in Lot	Triplicate from Each Lot
5. Water Content	NA	As per BPCR
Compression		
1. Compression M/C - Operation Parameter	Not Exceeding 2 hrs.	Twice in Shift
2. M/C Speed	Not Exceeding 1 hr.	Twice in Shift
3. Appearance, Description, Tablet individual Weight and Avg Weight.	Twice in Shift	Twice in Shift
4. Compression M/C - up to 37 Station	Not Exceeding 1 hr.	Twice in Shift
5. Compression M/C - More than 37 stations	Not Exceeding 1/2 hr.	Twice in Shift
6. Disintegration time, Friability, Thickness, Hardness, Dispersibility	Twice in Shift	Twice in Shift

1. How can Lean Six Sigma tools be implemented in pharmaceutical dosage form manufacturing to enhance product quality and process parameters?
2. What critical quality attributes/parameters play an important role in the improvement of yield and productivity? And how to provide a solution to it?
3. What kind of statistical tools can be used at each stage of OE?

2 Review Methodology

In this review, the pathway is decided by using the LSS technique and tools. The DMAIC method is used to carry out the project. DMAIC means "Define-Measure-Analyze-Improve-Control"[18]. Kottala N. (2013) discussed in their article regarding the impact of process parameters in the sustainable manufacturing of BT.[19]. Antony J (2022) performed a critical survey across the nations on the relationship of OE and critical success factors (CSF) or CQA in terms of implementation and found that the identification of CSF is very important through meta-analysis for sustainability.[20]

There are various methods to execute LSS as follows:

- Literature Survey
- Map the Shop Floor Activity
- Understanding Manufacturing Process
- Interaction with Stakeholders
- Data collection from BPCR (Executed BMR), Throughput data, SAP

2.1 Analytical methodology

Analytical methodology provides techniques to measure the process parameter and helps to evaluate it with statistical tools. Table 3 gives step wise process to follow DMAIC method and tools used.[21].

2.2 Define

The first step of DMAIC methodology is to define the process and the critical parameter, which helps to focus on the specific target[22]. Here are the steps given.

2.2.1. Defining Problem

Let's take an example where; the Low yield of BT which is one of the high-value & high-volume products in the industry.

Table 3. Analytical Techniques and Tools used in the DMAIC Method

Define →	Measure →	Analysis →	Improve →	Control
• Goal setting • Identification of scope of improvement • Project execution management • Stakeholder analysis • Training	• Value stream mapping/ Process mapping • Data collection plan • Statistical Analysis: • Control chart • Probability chart • Process capability chart • Graphical summary report • Pareto chart • flowchart	• Cause and Effect Analysis • Hypothesis testing • Statistical Analysis: • Pareto chart • Control chart • Graphical summary • Scatter plot	• SMED • POKA YOKE/ Mistake Proofing • 6S • Statistical analysis • Control chart- Before and After • Probability chart • Process capability chart • Graphical summary report • Pareto chart • flowchart	• Control plan • Gemba walk • Statistical Analysis: • Histogram • Control chart

2.2.2. Setting Goals

There is a standard method to find the scope of improvement to set the goal. One cannot set such a goal that is easily achievable or impossible to achieve [23].

To set the target first, we need to understand and analyze the trend of yield for the previous year's commercial batches. Table 4 has given details of calculation.

- Previous throughput data is used to draw lowest average yield (LAY) and highest average yield (HAY) and overall average yield (AY) of all previous commercial batches. Generally, previous one year throughput data is considered.
- The difference between the range of LAY and HAY is calculated. (Df)
- Calculate 50% and 75% of this difference value, respectively.
- Both values are added to the LAY, respectively.
- The Mean of these calculated values added to LAY is considered the new target or goal.
- To calculate the scope of improvement, the overall average yield is minus from the new target or goal.

Table 4. Method to Evaluate Scope of Improvement

Lowest Avg Yield %	Highest Avg Yield %	Difference btw AVG	Setting Standard	Avg Yield %	Goal %	Scope of Improvement %
LAY	HAY	Df	Df at 50% Df at 75%	AY LAY + Df at 50% LAY + Df at 75%	= Mean of (LAY + Df at 50%) & (LAY + Df at 75%)	= Goal -Avg Yield %

2.2.3. Stakeholder analysis

In a large-scale commercial project, there are many departments involved to run this project. From the manufacturing level to the plant head, are responsible for conduction of these activities. Hence, it is necessary to identify and label the responsibility and key actions of every stakeholder in this project. Table 6 will help to understand the influence of the stakeholders which are involved in the project and the desired level of impact on the project. [24], [25].

Table 5 clearly indicates that in the manufacturing process, fabrication and compression dept. play an important role in this project. The finance dept. is likely to be involved with greater degree of interest. The Project head plays key role in this action. The site head or plant head also highly influences the direction of the project. This type of project resembles the green belt carried out largely in industries.

2.2.4. SIPOC Technique

This is an OE tool used to identify the critical attributes involved in the process and in the project. SIPOC means "Supply-Input-Process-Output-Customer." A detailed analysis of the manufacturing process was carried out, and critical inputs and outputs of the process were defined in Table 6. This chart helped to specify the focus of project [26].

Table 5. Stakeholder Analysis

Stakeholder Group	Individual Stakeholder	Stakeholder Owner	Impact of Project on Stakeholder	Level of Influence on project	Desire Level of Support (1 to 9)	Key Stakeholder Action
Fabrication Dept Compression Dept	Individual Dept Manager	Production Head	High	High	9	Participate and involved in the project and review the progress
Coating Dept Packaging Dept			Medium	Medium	6	
Finance Owner	Finance Head	Project Head	High	High	9	Provide Cost benefit calculation and budget
Site Lead	Plant Head	Plant Head	High	Medium	8	Remove roadblocks in Project

2.3 Measure

After defining the critical parameters of the process, Process Stability, Process Normality and Process Capability are measured using Control Charts, Probability Plots and P- Value i.e., Pearson Correlation Value. This measuring of parameters and yield will provide guidance to initiate the change in the process[27]. In the manufacturing of BT, fabrication and compression play important role as coating and packaging are likely to be done as per conventional tablets. At the fabrication stage, two different layers are manufactured with different granulation techniques, such as dry mixing, wet granulation, compaction, etc. It is necessary to understand at which stages of the manufacturing process how much loss occurs, and which stage causes major loss. Pareto charts, which run on the 80/20 rule, can determine loss by stages and their contribution in total loss. Once a major loss-causing stage is determined, it is easy to analyze factors causing loss[28].

2.4 Analysis

Analysis of each defined critical parameter is done at this stage. If an industry has implemented a change or revised a process parameter, it is analyzed by DMAIC methodology. In this case, 'Two-step' analysis should be carried out at this stage; one is before change, and one is after change[29].

As discussed at the Measure stage, the higher loss occurs i.e., the compression stage and fabrication stage followed by the coating and packaging stage. A detailed analysis of losses should be carried out using a Pareto chart. Now, this study focuses on loss that occurs at compression stages, as this stage involves very critical parameters such as machine type and fabrication yield. The loss at the granulation stage is minimal as a result of bulk manufacturing and fewer critical parameters. This analysis is necessary to understand the types of loss at compression stages and their possible reasons[30].

At the compression stage there are basically two types of yield loss that occur, i.e., tablet defects and loss due to manufacturing. Tablet defects such as sticking require frequent cleaning of tools.

Analyzing the Yield Loss:

The focus was on losses at manufacturing stages; these are categorized into two types: one is accounted loss, and the other is unaccounted loss.

Accounted loss: These losses are measurable, and traceable from 'Batch Reconciliation Page', hence termed as 'accounted loss.' There are categories as per stages of compression. There are 3 types of accounted loss, i.e., setting loss, in-process loss, and leftover. Total accounted loss is the sum of setting loss, in-process loss, and leftover.

Setting Loss: In the tablet compression process, the initial setting of parameters like hardness, and tablet weight plays an important role. This setting is important to gain the desired weight and hardness of the tablet. The loss occurs during this weight adjustment called setting loss. In the case of BT there will be two separate losses for two separate layers. In a BT, first layer is set till the desired weight is achieved. And, then the second layer is added, set and checked for parameters by the production and QA department.

Table 6. SIPOC Technique

Supplier	Input	Process	Output	Customer
Warehouse	RM API RM Excipients BMR	Dispensing	Weighed Material	Verification
		↓		
Verification	Verified Weighed Material Equipment Utilities BMR	Sifting	Sifted Material	1. Granulation 2.Blending
		↓		
1.Shifting (Layer 1)	Sifted Material Equipment/ Utilities BMR	Wet Granulation	Granules	Blending (Layer 1)
		↓		
1. Granulation (Layer 1) 2.Shifting (Layer 2)	Granules/ Shifted material Equipment Utilities BMR	Blending	Blend Material	Compression
		↓		
Compression	Blend Material Equipment Utilities BMR	Compression	Tablets	Coating
		↓		
Coating	Tablets Equipment/ Utilities BMR Equipment/ Utilities	Coating	Coated Tablets	Packaging
		↓		
Packaging	Coated Tablets Equipment/ Utilities BMR	Packaging	Packed Product	FG warehouse

In-process loss: The loss occurs during compression process, such as rejection after stoppage, rejection due to metal detection, etc.

Leftover: It includes leftover granules or power, i.e., non-compressed material left in the hopper, in drums.

Unaccounted Loss: This loss is not measurable and traceable at the compression stage hence termed as unaccounted loss. This is calculated from the difference of total loss and accounted loss. The total loss is the standard batch size minus yield. There are many factors causing such loss; generally, at compression stage, the reason behind this loss is suction from exhaust ducts, spillage, machine consumption, etc.

To identify the major loss, a Pareto chart is used. For further analysis of individual loss control charts and histograms are used. This chart helps to identify the upper critical limit (UCL) and lower critical limit (LCL).

2.5 Analyzing Productivity

To understand the relationship between Productivity and Yield Improvement, Scatters plots are used. Productivity directly affects the yield value[31].

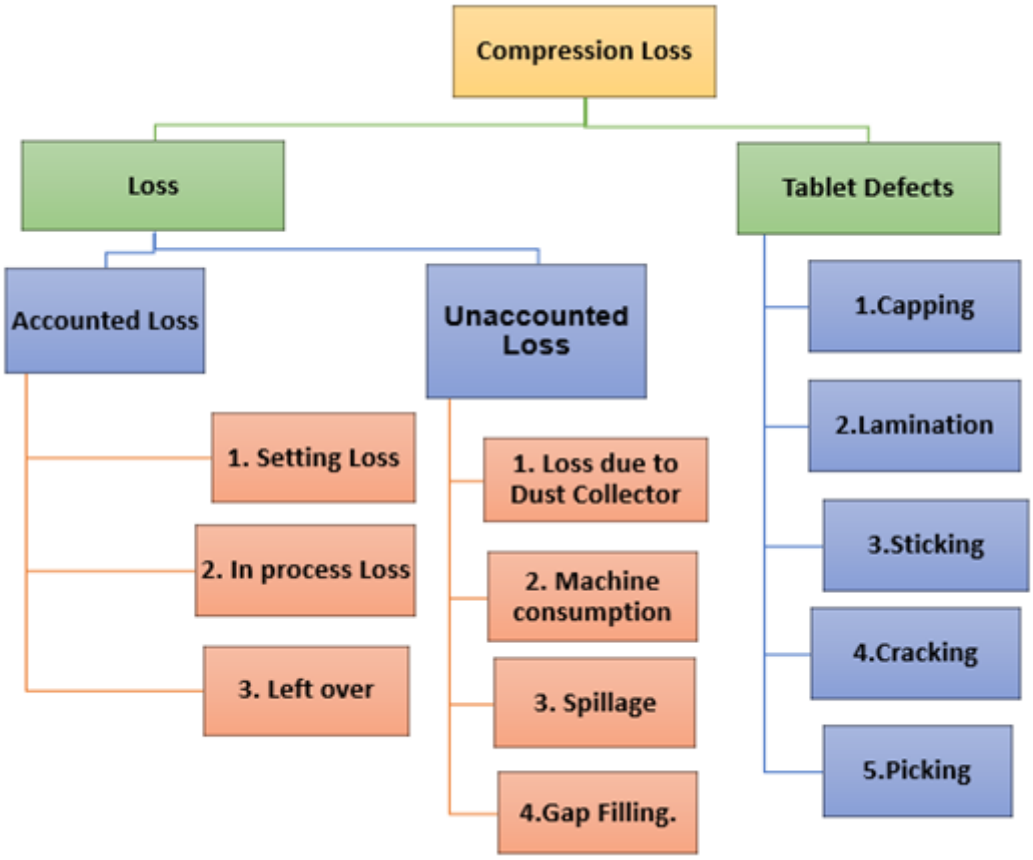

Fig 2. Types of Losses at Compression Stage

2.6 Improvement

In the manufacturing process, a change or revision of a process parameter is implemented to the improve process. To evaluate improvement due to the change, there are various statistical tools used e.g., Probability Plot and Process Capability Report. The CPK value, i.e., the Process Capability Report, determines whether the process is improved or not [32]. To understand the level of improvement, 'Cpk' values lie in the range of less than 1 as low improvement; between 1 to 1.33 as marginal improvement and greater than1.33 as Capable process for improvement.

2.7 Control

It is important to monitor the process after change has been implemented. An identification of the critical parameter that needs to be monitor is necessary. Hence, continuous verification assures stability of the new process [33], [34].

3 Overview

The application of Lean Sigma techniques shows us major changes in yield and productivity. Those changes are expected and implemented in the controlled fashion [35]. LSS gives a tool to identify the level & type of change for improvement and at which stages of manufacturing it is required. It is named Cause and Counter Measure Chart. Table 7 and Table 8 give detail insight on factors causing loss, its probable causes and solutions are also recommended.

The Cause and Counter Measure Chart give detailed insight into each parameter which caused the losses and their probable solution.

Table 7. Bilayer Tablet Compression Loss Cause and Counter Measure Chart for Accounted Loss

Bilayer Tablet Compression Loss Cause and Counter Measure Chart					
Type	**Sub type**	**Factor**		**Probable Causes**	**Recommended Solutions**
		Machine or Process Factor	**Product Factor**		
A. Accounted Loss	1. Setting Loss	Second layer setting		Unskilled operator	Training for unskilled operators to improve skills
					Skilled operator set the batches
		Machine stoppage		Power cut off	Provision for power back up
	2. In-process Loss	Initial rejection after m/c stoppage		Machine breakdown	Regular machine maintenance to avoid breakdowns
		Operator preoccupied with other activities		Operator is running to collect production aids	Required production aids should be in place
		Shift change		Operator left for meal or bio-break	Simultaneously two skilled operators should be working in area alternately
			Tablet Defect	Higher or lower moisture content in powder material	LOD And Moisture Content should be maintained at fabrication level only
				Defected tooling or improper setting of tools	Calibrated tools should be used
		IPQA clearance between running shift		Twice in shift – Frist layer Withdrawn multiple samples	Operator should be skilled to avoid excess loss during first layer weight check
	3. Leftover	One layer left higher than another layer		Higher loss at fabrication stage for either layer	Ratio of layers should be managed considering loss ratio
			Improper setting of tablet weight for individual layer	Skilled operators should adjust the weight ratio	

3.1 Results and Findings

Let's first discuss the factors related to machine setting. We have taken the example of BT, in which adjustment of the ratio of the first layer and the second layer is crucial, considering the losses that occur at different stages, ultimately to avoid leftovers is necessary[36].

As seen in CC&M chart, the major reasons for unaccounted loss are dust collector, suction system, and spillage. A Closed compression system will help to avoid these losses.

A uniform blend keeps compression parameters throughout the compression process, which leads to the minimum loss. Less compression time (Batch time) results in minimum stoppage of the machine, which leads to an improvement in yield[37].

The performance of individual stakeholders holds immense importance. Planning large campaign batches will avoid repetitive losses[38]. The decision of conversion of manual loading and unloading to automatized process at the management level and implementation at the operator level will also play an important role[39]. To successfully execute the OE project, like yellow belt, green belt, or black belt root cause analysis, risk management, continuous management support through funding and expert advice are required.[40]

Here are few takeaways while implementing OE

- Operational excellence is not just a scissoring tool to cut down wastage and to improve yield[41].
- OE provides various tools to analyze the critical area of improvement and serve to improve the overall quality of the product and manufacturing process[42].
- OE plays an important role from the supply chain dept to the finished goods store[43].
- OE applies to the planning of throughput manufacturing to the detail of manpower calculation[44].

Table 8. Bilayer Tablet Compression Loss Cause and Counter Measure Chart for Unaccounted Loss

Bilayer Tablet Compression Loss Cause and Counter Measure Chart					
Type	**Sub type**	**Factor**		**Probable Causes**	**Recommended Solutions**
		Machine or Process Factor	**Product Factor**		
B. Unaccounted Loss		Machine consumption		Type Of arrangement for Recirculation of material	Selection of Accurate Type of Machine
		Loss Due to Dust Collector in Area		Suction Pressure at Dust Collector	Maintained the suction Pressure
		Loss Due to Dust Collector attached To Compression Machine			
		Spillage		Unskilled Operator	Training to the Operator
				Improper Tool Setting	Calibration and Validation of Machine Tools
				Powder Characteristics	Notify the F&D dept.
		IPQA Test Sample		The exact Amount of test sample is not with draw for testing	The optimum Test Sample should be withdrawn and should be mentioned in BMR
			High Amount of Fine or Under-sized Material	Powder Characteristics	Amount of Fine Should Be controlled At Fabrication Stage only
				Improper Sifting at Fabrication Stage	
				High Amount of Lubricant	Training to the Operator

This study gives brief about scenario of pre and post OE implementation. An Industry facing challenges regarding building a quality culture among all levels of hierarchy, material handling and management, keeping sales demand, raw material shortage, batch failures, number of OSS & OOT, traceability of material and documents, achieving overall equipment efficiency and higher down time, recall and rework, optimum utilization of funds, issues with technology transfer and scalability, and waste management can be addressed with OE implementation. OE tools ensure increase in process efficiency (by 20-40%), cost reduction (2-5%), waste reduction (10-13%), improve product quality and compliance (up to 30%), skill enhancement and culture transformation, enhance customer satisfaction (by 30%).

4 Conclusion

A bilayer tablet is an oral solid dosage form that comprises the critical manufacturing process. Operational excellence provides various tools to analyze the critical area of improvement and serves to improve the overall quality of the product and manufacturing process. This study interprets the critical quality attribute that needs to be observed closely to increase the final yield of pharmaceutical products. The yield and productivity are the most important and direct affecting parameters to the overall cost of the manufacturing. Hence, focusing on this area, organization can reduce the manufacturing cost and increase production in terms of volume and sales. OE tool also serves to understand manpower allocation and skills. OE helps to improve JIT (Just in Time). Statistical interpretation leads to identification and analysis of the causes of loss, which need to work upon.

This study helps establish a correlation between product nature and process parameter for yield and product improvisation. It identifies the loss, defect, and breakdown in product as well as process. Ultimately, yield and productivity improvement will provide service and product to customers at a cheaper rate.

In this era of artificial intelligence and machine learning, implementation of OE and execution of such project at industry level will be fruitful and will bring more business excellence.

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