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PROCESS OPTIMIZATION, TROUBLESHOOTING OF TABLET PROCESS AND RISK ASSESSMENT

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ABSTRACT

The synopsis entitled "Process Optimization, Trouble Shooting of Tablet Process and Risk Assessment" is meant to improve manufacturing efficiency, reduce costs, and ensure product quality. Pharmaceutical manufacturers are seeking innovative solutions to optimize their manufacturing processes and troubleshoot potential issues. Process optimization involves first Identifying potential Issues, recognize common problems that can occur during tablet manufacturing, while Trouble shooting of tablet process involves various methods/ approaches to troubleshoot issues during tablet manufacturing and Risk Assessment involves conducting a risk assessment to identify potential hazards and mitigate risks. Process optimization uses various methods using the classic methodology by conducting experimentation followed by optimization. Certain techniques by using mathematical representation are also being followed. Troubleshooting is the diagnosis of symptoms of malfunction, and the process of determining and remedying the causes of these symptoms. There are various tools such as Failure Mode and Effect Analysis (FMEA) and Fault Tree Analysis (FTA) etc. for the trouble shooting. Risk assessment is an objective evaluation of risk which involves severity of harm, probability of occurrence and degree of detection of non-conformance. The test results of the model drug API are found to be meeting the predetermined specifications in accordance with the pharmacopoeia monograph. Similarly the in process results of various significant manufacturing steps and finished product meets the predetermined specification. The various remedial methods for each of the trouble shooting points are established. Based upon the optimized process very less number of trouble shooting are triggered leading to enhanced productivity and increased compliance. In addition the process automation techniques bring enhanced quality compliance.

KEYWORDS: Optimization, FMEA, FTA, Troubleshoot, Manufacturing, Risk Assessment.

1. INTRODUCTION

The pharmaceutical industry is under increasing pressure to improve manufacturing efficiency, reduce costs, and ensure product quality. Regulatory agencies, such as the US FDA and the European Medicines Agency, have implemented guidelines and standards to ensure the quality and safety of pharmaceutical products.

This project examines the application of process optimization and troubleshooting techniques in tablet manufacturing, with a focus on improving manufacturing efficiency, product quality, and regulatory compliance
This project focuses on process optimization and troubleshooting techniques in tablet manufacturing, aiming to identify and mitigate potential problems, and improve overall manufacturing efficiency.

2. MATERIALS AND METHODS

2.1 Process Optimization

The term Optimize is outlined as “to create perfect” it is utilized in pharmacy relative to formulation and process concerned in formulating drug product in varied forms.

2.1.1 Types of Optimization methods

- Evolutionary operations
- Simplex method
- Lagrangian method
- Search method
- Canonical analysis

2.1.2 Optimization of the process includes

- Initial risk assessment for process development.
- Equipment’s used at each processing steps and there operating parameters that were monitored at lab scale
- Process development studies
- Final process and formula
- Stability study
- Update risk assessment for drug product and manufacturing process
- Process map for manufacturing

2.2 Troubleshooting of pharmaceutical product

Troubleshooting is the identification of diagnosis of "trouble" in the management flow of a corporation or a system caused by a failure of some kind.
The problem is initially described as symptoms of malfunction, and troubleshooting is the process of determining and remedying the causes of these symptoms.

2.3 RISK ASSESSMENT

Risk assessment involves objectively evaluating risk by considering both potential loss and probability of occurrence. These elements can be difficult to measure, and errors are common. High-impact, low-probability risks are often treated differently than low-impact, high-probability ones, despite both being theoretically equal in priority.

In pharmaceuticals, manufacturing and using drug products inherently involve risks, with quality risk being one part. Maintaining consistent product quality throughout the lifecycle is essential.

Quality risk management

Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. According to ICH Q9, pharmaceutical quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of a medicinal product across the product life cycle.

Risk identification is a systematic use of information to identify hazards. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm(detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

2.4 Risk Management Methodology and Tools

- Basic risk management facilitation methods (flowcharts, check sheets, etc.);
- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering
- Supporting statistical tools.

Risk assessment using FMEA: FMEA provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance.

Steps:

1. Selection of the process
2. Review of the process
3. Brainstorm potential failure modes
4. List of potential effects of each failure mode
5. Assign a severity rating for each effect
6. Assign an occurrence rating for each failure mode
7. Assign a detection rating for each failure mode and effect
8. Calculation of the risk priority number (RPN) for each effect: (RPNs) = O×D×S
9. Prioritize the failure modes for action

10. Taken action to eliminate or reduce the high risk failure modes
11. Improvement index (II): II = (RPN before improvement) / (RPN after improvement)

Table 1: Score scale for frequency of occurrence.

Failure	Probability of failure	Occurrence Ranking
Very High: (Failure is almost inevitable)	≥ 1 in 2	10
	1 in 3	9
High: (Repeated failure)	1 in 8	8
	1 in 20	7
Moderate: (Occasional failure)	1 in 80	6
	1 in 400	5
	1 in 2000	4
Low: (Relatively few failure)	1 in 15000	3
	1 in 150000	2
Remote: (Failure is unlikely)	1 in 1500000	1

Table 2: Score scale for probability of detection.

Detection	Criteria	Detection anking
Impossible to detect	No known techniques available	10
Remote detection	Only unreliable technique available	9
Very slight detection	Providing durability tests on products with system components installed	8
Slight detection	On product with prototypes with system components installed	7
Low detection	On similar system components	6
Medium Detection	On preproduction system components	5
Moderate detection	On early prototype system elements	4
Good detection	Simulation and modeling in early stage	3
High chance of detection	Proven analysis available in early design stage	2
Certain to detect	Proven detection methods available in concept stage	1

Table 3: Score scale for severity.

Severity	Effect	Severity Ranking
Hazardous without warning	Without warning, people can get severely wounded	10
Hazardous with warning	May cause hazards, with warning	9
Very high	Loss of primary function	8
High	Highly reduced level of performance	7
Moderate	Reduced level of performance	6
Low	Slightly reduced level of performance	5
Very low	Defect noticed by most of the customers	4
Minor device	Defect noticed by average customers	3
Very minor	Defect noticed by discriminating customers	2
None	Almost no effect	1

3. RESULT AND DISCUSSION

3.1 Process Optimization and Risk assessment

- The term Optimize is defined as “to make perfect”. It is used in pharmacy relative to formulation and processing involved in formulating drug products in various forms.
- Final product not only meets the requirements from the bio-availability but also from the practical mass production criteria.

Table 4: Test results of Model drug—Cefpodoxime Proexetil.

Test	Specification	Results
Physical appearance	A white - off white powder with characteristic odour	A white powder with characteristic odour
Melting point	Between 211 - 213ºC	212 ºC
IR spectra	Infrared (IR) spectrum exhibits characteristic peaks that can be used for identification and analysis, with notable peaks around 2823.28, 1760.69, 1780.66, 1618.95, 1274.72, 808.992, and 693.28 cm^{-1}	Infrared (IR) spectrum exhibits characteristic peaks that can be used for identification and analysis, with notable peaks around 2823.28, 1760.69, 1780.66, 1618.95, 1274.72, 808.992, and 693.28 cm^{-1}
UV	The material should exhibit UV absorption maxima at around 232-235 nm and 260.8 nm.	The material exhibits UV absorption maxima at around 232-235 nm and 260.8 nm.
Solubility	The raw material poorly soluble in water, with a solubility of around 0.4 mg/mL, but soluble in organic solvents like ethanol, methanol, DMSO, and acetonitrile.	The raw material is poorly soluble in water, with a solubility of around 0.4 mg/mL, but soluble in organic solvents like ethanol, methanol, DMSO, and acetonitrile.
Specific rotation	Between +35.0◦ and +48.0◦	+40.0◦
Water by KF	NMT 3.0%	1.8%
Residue on ignition	NMT 0.2%	0.12%
hromatographic Purity	Any other individual impurity NMT 0.5% Total impurity NMT 6.0%	Any other individual impurity is 0.12% Total impurity 2.3%
Residual Solvent	Should meet the <467>	Meet the requirement of <467>
Assay	Between 98.0 to 102%	99.8%

Table 5: In process test---Blend analysis.

Blend		
Test	**Specification**	**Results**
Bulk density(g/ml)	NLT 0.45	0.51
Particle size (sieve analysis)	NMT 60% (#40) and NMT 40% (#80)	56% over 40# 32% over 80#
L.O.D (1g/105ºC/2hr)	NMT 6.0	4.2
Assay (drug content)	95-105%	99.3%

Table 6: In-process test – Compression.

Stage: Compression		
Test	**Specification**	**Results**
Avg. Weight (mg)	300mg (291mg -309mg)	303mg
Uniformity of weight (%)	285.0 -315.0mg (± 5% of avg. Weight)	305mg
Hardness (N)	10.0- 16.0	12 N
Friability (% w/w)	NMT 1.0	0.56

Table 7: In-process test – Coating.

Stage: Coating		
Test	**Specification**	**Results**
Dissolution by UV	NLT 80 % (Q) the labelled amount of Cefpodoxime is dissolved in 30 min.	99%

Table 8: Process variables, Measure response and Acceptance criteria.

Process Steps	OPERATIONAL PARAMETERS		Measured Responses	Acceptance Criteria
	Control Variables	Value/ Range		
Sifting and milling	Sieve Size	Mesh # 22	Observations of extraneous matter (if any)	Absence of extraneous matter
	Screen size	1.0 mm		
	Mill speed	Fast speed (4500 rpm)		
	Blade Configuration	Impact Forward		
Premixing	Premixing Time (min.)	20	Recording of Parameters	Compliance to limits specified in the manufacturing Instructions.
Compaction and milling	Roller Speed (rpm)	5 - 8 (Target: 7)	Recording of Parameters	Compliance to limits specified in the manufacturing Instructions.
	Sieve Size	Mesh # 22 & # 60 & #16		
	Screen Size	1.5 mm (O.G) & 2.0 mm (Mill)		
	Blade Configuration	Knives Forward		
	Mill Speed	Medium Speed		
	Weight of granules	NLT 72 kg		
Sifting of Lubricant	Sieve Size	Mesh # 60	Observations of extraneous matter (if any)	Absence of extraneous matter.
Blending	Blending Time (min.)	10	Blend Uniformity	Compliance to acceptance criteria as specified in sampling plan.
Compression	Average Weight (mg)	269 – 281 (Target: 275)	In-process Parameters monitoring	Compliance to limits specified in the manufacturing Instructions.
	Uniformity of weight (mg)	261.25 - 288.75 mg (± 5 % of average weight)		
	Thickness (mm)	4.0 – 4.6 (Target: 4.3)		
	Hardness (kp)	6.0 – 14.0		
	Friability (% w/w)	NMT 1.0		
	Disintegration time (min)	NMT 15		
	Machine speed (tablets/min)	950 (800 – 1100)	Uniformity of Dosage Units	Compliance to acceptance criteria as specified in sampling plan.
Coating	Film Coating		Appearance	White to off-white, capsule shaped film coated tablets plain on both side
	Inlet Air temperature (ºC)	50 – 70 (Target: 60)		
	Pan speed (rpm)	2.0 – 5.0		
	Spray rate (g/min)	175.0 – 225.0 (Target: 200.0)		
	Drying after coating		Final Coat Weight Build Up	2.75 – 3.25 % w/w (Target: 3.0 % w/w)
	Inlet temperature (ºC)	Inlet temperature (ºC)		
	Drying time (min.)	Drying time (min.)		
	Jogging Time	Jogging Time	Dissolution	Compliance to acceptance criteria as specified in sampling plan.

3.2 Experiment design for evaluation of Blend and its impact upon Compression

The blend characters are evaluated by reviewing the compressibility index (Carr index) and the closely related Hausner's ratio which may predict powder flow characteristics as being affected by size and shape, material density, surface area, moisture content, and cohesiveness of powder.

The compressibility index and Hausner's ratio may be calculated using measured values of untapped bulk density and tapped bulk density.

Table 9: The compressibility index and the Hausner's ratio are interpreted as follows.

Compressibility Index (%)	Flow Character	Hausner's Ratio
1–10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Table 10: Cefpodoxime Proxetil blend data for evaluation of Flow properties.

Batch No	1	2	3	4	5	6	7	8	9
Hausner's Ratio	1.23	1.35	1.399	1.421	1.43	1.54	1.428	1.39	1.07
Carr's index	26	32.7	25.2	32.57	32.57	29.2	29	37.46	34

3.3 Risk assessment for Drug product

Failure Mode and effects

(S- Severity ranking, O- Probability of Occurrence, D- Probability of detection, RPN- Risk priority number)

Table 11: Failure mode, effect, cause, measure with RPN calculation.

Sr. No.	Failure Mode	Failure Effect	S	Failure Cause	O	Control Measure	D	RPN
1.	Receiving incorrect material	Contamination, cross contamination in raw material	8	Incorrect check during receiving of raw material	2	Approved Vendor	1	16
2.	Improper mixing	Non uniformity	7	Mistake in sieve no.	3	Proper checking, follow BMR	1	21
3.	Mixing time	Improper mixing	6	Equipment problem, time not followed as per BMR	2	Follow BMR	1	12
4.	Mixing speed	Improper mixing	6	Equipment problem, speed not followed as per BMR	2	Follow BMR	1	12
5.	Mixing load	Improper mixing	5	Load excess or less than equipment capacity	2	Follow BMR	1	10
6.	Compression	Improper compression force	7	Non uniform release of dose	2	Follow BMR /In-process Quality checks	1	14
7.	Compression	Improper compression force	6	Improper hardness, weight variation and thickness	2	Follow BMR/In-process Parameters	1	12
8.	Compression	Weight variation	6	Flow property of granules	7	Improve flow properties	1	42
9.	Coating	Poor film formation	8	Improper masking for appearance/drug release	6	Follow BMR/In-process Parameters	5	240
10.	Spraying	Development of droplets	6	Improper comp. air/peristaltic pump setting	5	Adjustment of spray gun	3	90
11.	Coating	Poor film formation	8	Improper Spraying/drying/gun to bed distance	6	Adjustment of pan load	1	48
12.	Coating	Breakage, color variation	8	Pan speed	5	Adjustment of pan speed	4	160
13.	Coating	Twinning,	8	Atomization pressure	7	Adjustment of atomization pressure	1	56

3.4 Troubleshooting of pharmaceutical product

- Troubleshooting is the identification of diagnosis of "trouble" in the management flow of a corporation or a system caused by a failure of some kind.
- The problem is initially described as symptoms of malfunction, and troubleshooting is the process of determining and remedying the causes of these symptoms.

3.6 Troubleshooting in API testing process:

- **Melting point---** Improper Melting point.
- **IR spectra ---** IR spectra does not meet the correlation coefficient
- **Solubility** --- Failing in solubility
- **Water by KF**--- Failing of water content
- **Residue on ignition**--- Failing on Residue on ignition
- **Chromatography**--- Failing in assay and chromatographic purity

3.7 Troubleshooting in manufacturing process:

- **Granulation**: **Dry granulation, Wet granulation and Direct compression**
- **Capping/lamination/chipping:** The top or bottom of the tablet fractures away or tablet separates into layers
- **Sticking/Picking:** Material adheres to the punch face or die
- **Weight and Content Variations:** Tablets deviate from the target weight or active ingredient content.

3.8 Risk assessment

The Raw material testing particularly the excipient chemistry is very vast, while only a portion of the excipient's chemistry are being analysed for its functional properties which are reported in the specifications. There are always certain challenges associated with the analysis since all samples are prepared by human (analyst) irrespective of engaging the most sophisticated instrumentation. The associated risk for Invalid Out of specification (OOS) generated due to human error possess threat to either delay in manufacturing the finished product or the investigation are always challenged during the inspection.

Certain analytical methods associated with Physical parameters such as Solubility, Particle size distribution and Particle shape depends upon the analytical method which are developed and validated in-house at time needs to be revised and filed with the regulatory agencies. This filing possess a risk of temporary stoppage of manufacturing finished product thus causing market dry and keeping patient waiting for the availability of the drug.

4. CONCLUSION

Tablets gave good release over time. Application of initial risk assessment and FMEA tool helped easy identification of critical quality attributes. Design of experiments was also useful in designing of proper experiments. It was concluded that the appropriate statistical design and optimization techniques can be successfully used in the optimizing process parameters in tablet compression. If Geometry of tablet presses are same then similar process parameters can be reproducible in all machine with minimal impact on tablet properties in terms of hardness, thickness, disintegration time and friability. Other variables like Turret Speed, Pre compression force and feeder speed does not have significant Impact on tablet properties.

The risk management program consists of four major components: risk assessment, risk control, risk review, and risk communication. All four components are essential. All the above methods should address the mentioned four basic components. Team selection and method selection are also playing a vital role in the risk management process, so care should be taken while selection of risk management team and method. FMEA is the preferable method for risk management in the pharmaceutical industry as FMEA analysis include higher reliability, better quality, increased safety and its contribution towards cost saving includes decreased development time and reduced waste and non-value-added operations.

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