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Process Validation And Risk Assessment Study of Loratadine Tablet

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Abstract:

The purpose of research was to study Prospective Process Validation Loratadine 10 mg tablet dosage formulation. Process Validation is the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering Quality products. Three consecutive batches of Loratadine 10 mg tablet manufactured as per the Batch Manufacturing Record. Collected samples at different stages like for sifting, blending, compression as mentioned in the sampling plan for individual process. Then sent for analysis, each parameter was analyzed and tested as per specifications and recorded the results, which were found wit in the limits. The results suggest that the all parameters are within the limits. All physical parameters like weight-variation, hardness and thickness, disintegration time, friability were found within the limits. So the manufacturing process intended for further batches. The process is validated as per specifications. Overall manufacturing processing parameters are analyzed and compared with the standard specifications, found within the limit and it was concluded as the parameters mentioned above validated as per BMR and BPR. The process validation data of Loratadine 10 mg tablets reveals that there was no significant variation between batch to batch and all the process variables were studied. Therefore, it can be concluded that the process of Loratadine 10 mg tablet Validated.

Key Words : Loratadine tablet, Prospective, Process validation,Risk assessment, Process parameters.

Introduction [1]:
Process Validation is the means of ensuringand providing documentary evidence that processes within their specified design parameters are capable of reliably and repeatedly producing a finished product of the required quality.

Principle[2]:
Process validation is a basic factor for drug product safety and quality and thus a fundamental component of the quality assurance system used by pharmaceutical manufacturers. The basic principle of Quality Assurance is that a drug should be produced that is fit for its intended use. Effective Process Validation contributes significantly to assure the drug quality; this principle incorporates the understanding that the following conditions exist:

Quality, safety, and efficacy are designed or built into the product. Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.

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Objectives[3-4]:
In addition to the individual equipment, the manufacturing process must be validated. The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency. Engineers should draft and execute a validation plan for the manufacturing process in order to satisfy guidelines. The validation plan usually involves just a PQ section. Just as equipment validation, after the initial validation, major changes will result in the need for subsequent revalidation.

Process validation will ensure a robust product which is more reproducible over time.

Types of Process Validation [4] :
The guidelines on general principles of process validation mentions four types of validation:
A) Prospective validation
B) Concurrent validation
C) Retrospective validation
D) Revalidation

Phases of Validation[5-7]:
The activities relating to validation studies may be classified into three phases:

Phase 1: Pre-validation phase or the qualification phase
Phase 2: Process validation phase (process qualification phase)
Phase 3: Validation maintenance phase.

Risk Assessment Study [8]:
"A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards." (ICH Q9)

Principles of Quality Risk Management
1. Two primary principles of quality risk management are:
2. The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
3. The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

Initiating a Quality Risk Management Process
Two primary principles of quality risk management are:
The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

Initiating a Quality Risk Management Process
Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk; Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment; identify a leader and necessary resources.

General Quality Risk Management Process

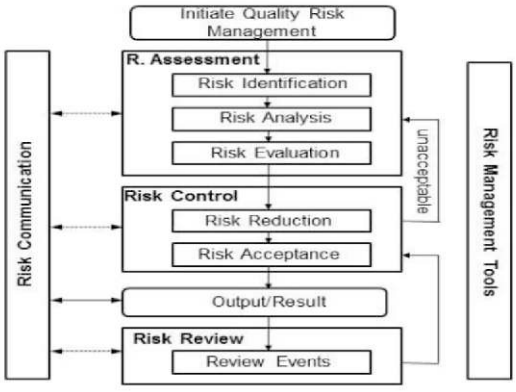

Figure 1: Overview of a typical quality risk management process

Risk Assessment
Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in section 5) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. 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 (delectability) 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.

Risk Control
Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control. Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detestability of hazards and quality risks might also be used as part of a risk control strategy.

Risk Management Methodology
Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes delectability of the risk.

Additionally, the pharmaceutical industry and regulators can access and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these 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 Management Methods and Tools
The purpose of this annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

Basic Risk Management Facilitation Methods
Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are: Flowcharts; Check Sheets; Process Mapping and Cause and Effect Diagrams.

Failure Mode Effects Analysis (FMEA)
FMEA provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

Materials & Methods:

Introduction:
Prospective process validation was performed on the three batches of Loratidine tablet. The three batches were labeled as (Batch A, Batch B, Batch C). The protocol includes list of raw materials, list of equipments used, critical process parameters, standard specification and acceptance criteria and sampling plan as given below. During the manufacturing process samples were collected and sent for analysis to Q.C. department.

Materials:
Loratadine,lactose,methyl paraben, propyl paraben, maize starch, colloidal anhydrous silica, magnesium stearate, purified talk, sodium starch glycolate, sodium lauryl sulphate, cross carmellose sodium.

List of Equipments:
Rapid mixturegranulator(HSMG),multi mill, fluid bed system, paste preparation kettle, octanol bladder, de dusting/ de burring machine, 31 station double rotatory compression machine, punch set round flat plain on both side, tablet inspection belt, weighing balance, vernier caliper, analytical balance, digital friability tester, disintegrating test app, ir moisture, tablet hardness tester.

Table 1: Product Detail

Product	Loratadine Tablet 10mg USP
Strength	10mg
Label claim	Each Uncoated Tablet Contains : Loratadine 10mg
Description	White flat circular bevel edged uncoated tablets plain on both side
Batch size	30,60,000 TAB (428.40kg)
Storage condition	Store in a Cool & dry place protect from light
Shelf life	36 months
Market	Export

Methods:

Validation Procedure
1. Three batches of 30,60,000 tablets batch size to be manufactured as described in the batch manufacturing record.
2. Current version of standard operating procedures to be followed.
3. Record the observations at compression stage in the data sheets.
4. Record the yield after coating.

Manufacturing Process
Sifting:
Loratadine is sifted using 20# SS Sieve while maize starch and cross carmellose sodium are sifted using 40# SS Sieve.

Dry Mixing:
Mixture of above ingredients are allowed for mixing for 15 minute at slow speed.

Binder preparation and addition:
Add purified water in Paste preparation kettle and boil it up to 90-100 ºC. Dissolve Sodium Methyl Paraben and Propyl Paraben in it. Dissolve Maize starch in purified water and make slurry. Add this slurry into paste vessel with constant stirring and make lump free paste. Allow paste to cool at room temperature.

Wet Granulation:
Add the binder slowly to the RMG and operate the RMG at slow speed for 5 minutes. When if required add additional purified water to obtain a proper granulated mass. Open the RMG discharge gate and unload the wet granulated mass at impeller fast and chopper fast mode into double poly bag placed in a container.

Wet milling:
Check integrity of 8 mm SS Screen before operation. Pass the wet mass through multi mill at medium speed and collect the milled granules in double lined polybag. Check integrity of 8 mm S.S Screen after operation.

Drying:
Dry the whole batch in FBD at 45-55 ºC temperature for 60-80 min.

Sifting:
Pass the dried granules through 20# sieves in shifter and

collect in container with double poly bag.

Dry Milling:
Check the integrity of 1.5 mm multi mill screen. Pass the retained granules at medium Speed and collect in double polybag placed in a container.

Lubrication:
Cross carmellose sodium and magnesium stearate pass through 40# sieve and collect in a poly bag. Then load the sifted material into Octagonal Blender. Load the milled granules into Octagonal Blender then after operate the blender for 30 min. collect the lubricated granules in Double poly bag in Polyethylene lined containers.

Compression:
Compress the granules as per following specifications. :
- Machine: 37 station double Rotary compression machine
- Punch: Standard Concave
- Upper Punch: Plain
- Lower Punch: Plain.
- Diameter: 10.0 mm.
- Thickness: 5.30 mm
- Hardness: NLT 2.0 kg/cm2.
- Friability Test: NMT 1.0% w/w
- Average Weight of Tablet: 390.00 mg.
- Weight Variation: NMT ± 5% of Average Weight.

Manufacturing Process:

Table 2 :Risk Assessment For Drug Product & Manufacturing Process Parameters

STAGE	RISK INVOLVE	IMPACT	CURRENT CONTROL
Shifting	1.Sieve Integrity 2.Improper Sieve Size 3.Improper Sifting	1.Foreign Matter 2.Product Quality	1.Intactness of sieve was checked prior and after sifting 2.Sieve size was ensured as per given BMR 3.Well trained personnel
Granulation	High /Low Spray rate	1.Hardness 2.Friability 3.Disollution 4.Disintegration 5.Garnules Quality	1.Spray rate limit according to BMR 2.Spray rate calibration was done prior to spraying
Blending	1.Loading and mixing Pattern 2.RPM and Time Variation	1.Blend Uniformity 2.PSD	Blending Time , RPM , Materials loading and mixing pattern, Qualification were ensured from BMR
Compression	1. Improper selection of tooling 2.Wrong Machine Set up 3.Contamination of Drug 4.Force Feeder RPM	1.Product Appearance 1.Hardness 2.Thickness 3.Physical appearance 4.Disintegration time 5.Capping 1.Product Quality due to machine lubricant 1.Weight Variation	1.SOP was available for machine set up 2. Instruction for verification of the process machine set up at the time of startup clearance was included in BMR. Dust cup were used for upper punch during compression process and same was incorporated in BMR. Limit As per BMR
Lubrication shifting	1.Sieve Integrity 2.Improper Sieve Size	1.Foreign Matter 2.Product Quality	1.Intactness of sieve was checked prior and after sifting 2.Sieve size was ensured as per given BMR

Results and Discussion:

Status of Equipment and Instruments Used During Manufacturing:
All equipment and instruments were maintained, qualified and calibrated before use.

Sifting: Integrity of Sieve Before and After Use
For loratadine 20# and for excipients 40# was used.No damage of sieve was observed. There was not any particle on sieve. No foreign particles were observed. Integrity of the sieve before and after use was found intact.

Dry Mixing
Speed of impeller and chopper was slow.

Table 3: Data of Dry Mixing

Test parameter	Batch	Mixing time (min)			Acceptance criteria
		05	10	15	
%RSD	A	1.63	0.68	0.97	NMT 2%
	B	0.58	0.95	0.89	
	C	0.60	0.57	0.98	

Table 4: Data of %LOD at the end of drying

Test parameter	Sample point	Observation (in minutes)									Acceptance criteria
		Batch-A			Batch-B			Batch-C			
		20	30	40	20	30	40	20	30	40	
Loss on drying (%)	Top	1.86	1.65	1.50	2.12	1.75	1.51	1.94	1.68	1.56	1-3%
	Middle	1.95	1.79	1.68	2.06	1.69	1.50	2.25	1.50	1.59	
	Bottom	1.89	1.33	1.52	2.32	1.65	1.54	1.98	1.78	1.54	

It was evident that the dry mixing throughout the sampling locations has been carried out and at 10 min % assay achieved near target value. %RSD of loratadine tablets for all three validation batches were found within the limit of acceptance criteria. So dry mixing was performed for 10 minfor routine manufacturing batches.

Table 5: Data of Blend uniformity

Test Parameter	Batch	Mixing time (min)			Acceptance criteria
		05	10	15	
%RSD	A	0.78	0.75	0.49	NMT 2 %
	B	0.67	0.71	0.69	
	C	0.63	0.78	0.64	

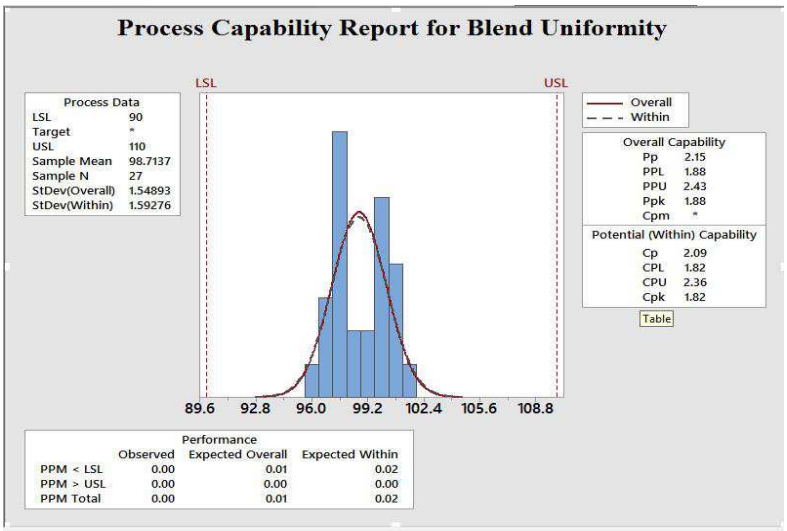

Figure2: Process Capability Report for Blend Uniformity

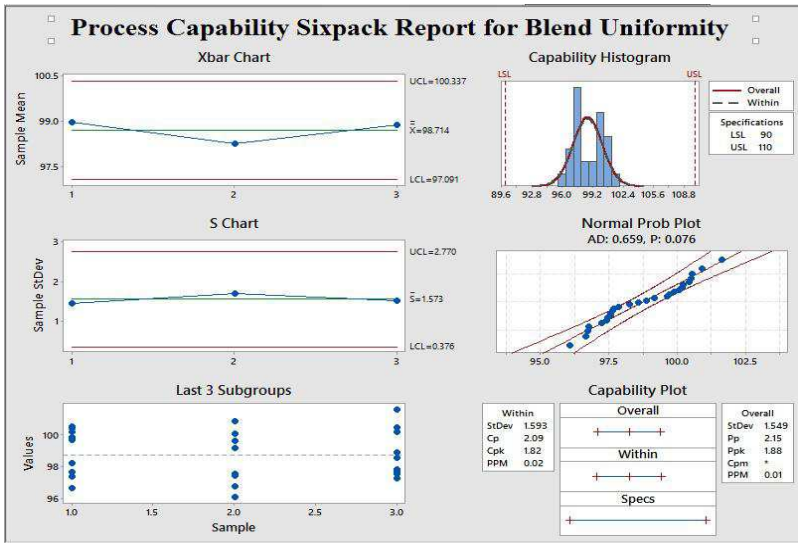

Figure 3 Process Capability Sixpack Report for Blend Uniformity

Interpretation:

Table 6: Interpretation of Results

Sr. No.	Capability Indices	Values
1	Cpk Value	1.82
2	X-bar	98.71
3	Defects PPM Level	00.1

From above analysis, it is observed that the Cpk value, X-bar value of Studied parameter for all three batches were found within limit and the Defects PPM value found to be 0.01 which shows that all the parameter meet specification under Six sigma level. So, it is concluded that the process is capable to meet its predetermined specification.

Table 7: Data of Hardness of Tablet of all three batches:

Hardness									
Specification	NLT 3.0 Kg/cm2								
Control Variable	Batch-A			Batch-B			Batch-C		
Speed (RPM)	12	25	40	12	25	40	12	25	40
	RPM	RPM	RPM	RPM	RPM	RPM	RPM	RPM	RPM
in/Max	5.1	4.2	3.6	4.5	4.8	3.5	4.8	4.3	3.6
	/	/	/	/	/	/	/	/	/
	5.5	5.1	4.0	5.1	5.3	3.8	5.3	4.8	3.9

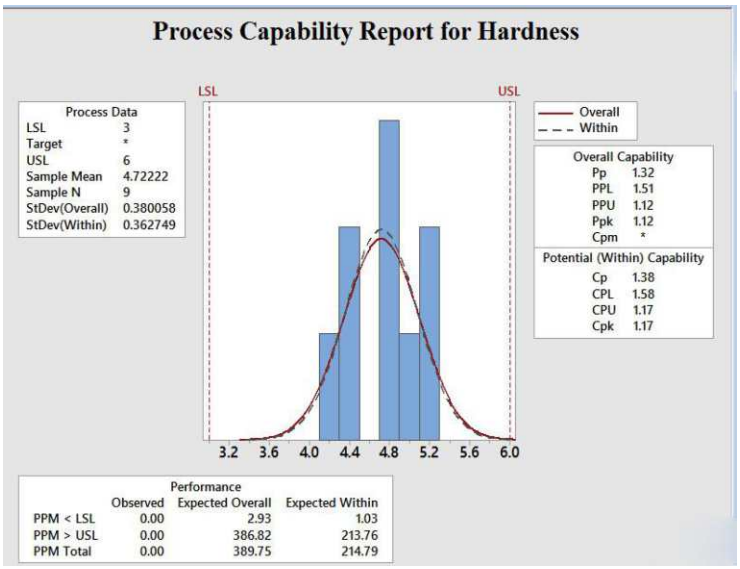

Figure4: Process Capability Report for Hardness

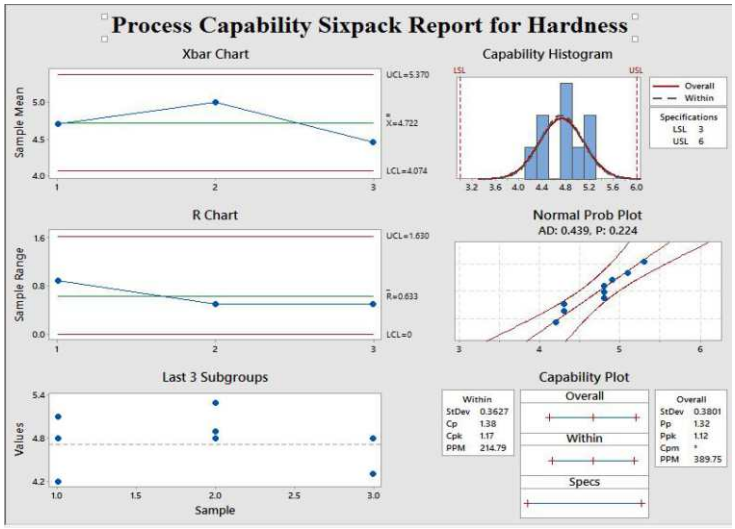

Figure5: Process Capability Six pack Report for Hardness

Interpretation:

Table 8: Interpretation of Results

Sr.No.	Capability Indices	Values
1	Cpk Value	1.17
2	X- bar	4.72
3	Defects PPM Level	389.75

From the above capability analysis, it is observed that the Cpk value is 1.17which is more than 1. And from the above capability analysis X-bar value of studied parameter for all three batches found 4.72 which means process is capable to produce product meeting it specification and defect PPM total value found to be 389.75 which shows that all the parameters meet specification under six sigma level. So, it is concluded that the process is capable to meet its predetermined specification.

Table 9: Data of Thickness of Tablet of all three batches

Thickness									
Specification	2.7mm+0.2mm (2.5mm-2.9mm)								
Control Variable	Batch-A			Batch-B			Batch-C		
Speed (RPM)	12 RPM	25 RPM	40 RPM	12 RPM	25 RPM	40 RPM	12 RPM	25 RPM	40 RPM
Min/Max	2.68 / 2.71	2.70 / 2.72	2.72 / 2.74	2.68 / 2.71	2.69 / 2.72	2.69 / 2.73	2.68 / 2.70	2.71 / 2.72	2.71 / 2.74

Table 10: Data of Diameter of Tablet of all three batches

Thickness									
Specification	7.0mm+0.1mm (6.9mm-7.1mm)								
Control Variable	Batch-A			Batch-B			Batch-C		
Speed (RPM)	12 RPM	25 RPM	40 RPM	12 RPM	25 RPM	40 RPM	12 RPM	25 RPM	40 RPM
Min/Max	6.98 / 7,02	7.00 / 7.01	7.00 / 7.03	6.98 / 7.02	6.98 / 7.02	7.01 / 7.04	6.98 / 7.04	6.99 / 7.02	7.01 / 7.04

Table 11: Data of Disintegration Time of Tablet of all three batches

Thickness									
Specification	NMT 10 min								
Control Variable	Batch-A			Batch-B			Batch-C		
Speed (RPM)	12 RPM	25 RPM	40 RPM	12 RPM	25 RPM	40 RPM	12 RPM	25 RPM	40 RPM
Min/Max	2'38" / 2'45"	2'32" / 2'35"	2'15" / 2'30"	2'32" / 2'37"	2'23" / 2'30"	2'11" / 2'24"	2'35" / 2'44"	2'32" / 2'34"	2'19" / 2'30"

Table 12: Data of Dissolution Time of Tablet of all three batches

Thickness									
Specification	NLT 80%								
Control Variable	Batch-A			Batch-B			Batch-C		
Speed (RPM)	12 RPM	25 RPM	40 RPM	12 RPM	25 RPM	40 RPM	12 RPM	25 RPM	40 RPM
Min/Max	97.56 / 100.32	98.56 / 103.68	99.69 / 101.56	98.65 / 102.56	99.65 / 102.80	98.63 / 102.64	98.64 / 103.09	98.51 / 100.56	99.36 / 102.69

Table 13: Data of Assay of Tablet of all three batches

Test parameter	Batch	Mixing time (min)			Acceptance criteria
		05	10	15	
%RSD	A	1.63	0.68	0.97	NMT 2%
	B	0.58	0.95	0.89	
	C	0.60	0.57	0.98	

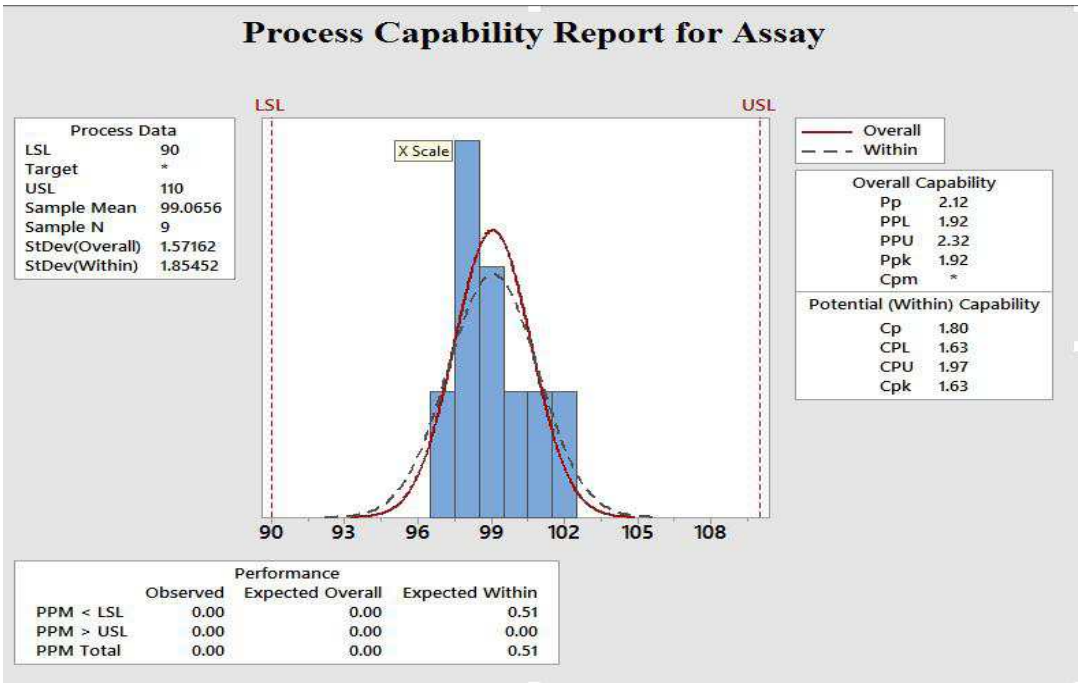

Figure 6 : Process Capability Report for Assay

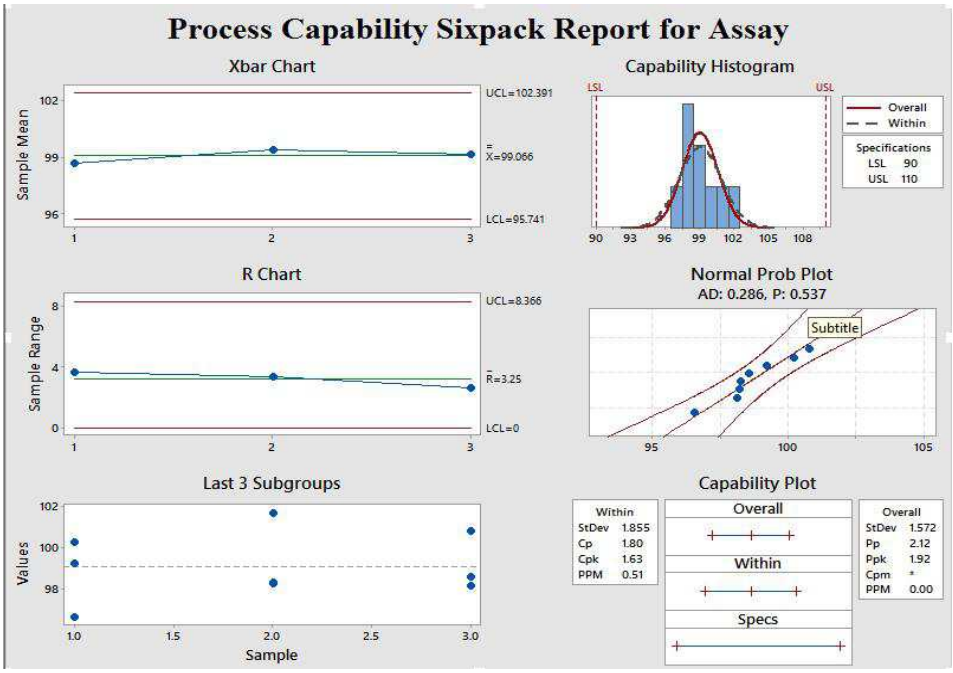

Figure 7 : ProcessCapability Six-pack Report for Assay

Interpretation:

Table 14: Interpretation of Results

Sr.No.	Capability Indices	Values
1	Cpk Value	1.63
2	X- bar	99.06
3	Defects PPM Level	0.00

From the above capability analysis, it is observed that the Cpk value is 1.63which is more than 1. And from the above capability analysis X-bar value of studied parameter for all three batches found 99.06 which means process is capable to produce product meeting it specification and defect PPM total value found to be 0.00 which shows that all the parameters meet specification under six sigma levels.So,it is concluded that the process is capable to meet its predetermined specification.

Table 15: Finished product tests and observations

Test Parameter	Observation			Standard
	Batch-A	Batch-B	Batch-C	
Description	White flat circular bevel edged uncoated tablets plain on both side			White flat circular bevel edged uncoated tablets plain on both side
Identification	The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of std. preparation obtained in the assay.			The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of std. preparation obtained in the assay.
Avg wt. (mg)	140.52mg	139.11mg	140.86mg	140.0 mg ±2 % w/w (137.2 mg to 142.8 mg)
Uniformity of wt.	± 5% of average wt.			± 5% of average wt.
Diameter (mm)	7.06	7.08	7.04	7.00 mm + 0.10 mm (6.90 mm to 7.10 mm)
Thickness (mm)	2.76	2.88	2.72	2.70 mm ± 0.20mm (2.50 mm to 2.90 mm)
Hardness (kg/cm^2)	3.4	3.6	3.8	NLT 3.0 kg / cm^2
Disintegration time (min'sec")	2'36"	2'45"	2'47"	NMT 10.0 min
Dissolution (%)	98.56 %	99.61%	101.15 %	NLT 80%
Uniformity of dosage unit	103.80%	96.85%	103.77%	90 % to 110% of the labeled amount
LOD	1.56%	1.67%	1.89%	1-3%
Assay of Loratadine	99.56%	101.92%	99.66%	90.0 % to 110.0 % of the labeled amount

Discussion:

Validation of Sifting Process:

All materials were passed through 20# & 40 # SS sieve in vibro Shifter. Damage was not observed before and after passing raw materials through vibro shifter during shifting of three batches. Hence, shifting process was validated.

Validation of Dry Mixing and Granulation Process:

After completion of the shifting raw materials were mixed in Octagonal. Samples were collected from different point from Octagonal and check for description, blend Uniformity and % RSD. All the three batches were found to have powder raw materials description as per the specification, blend uniformity between 90.0- 110.0%. Then granules were mixed completely within 20 min at slow speed. Binding was proper observed in all three batches. Hence, Dry mixing and granulation process was validated.

Validation of Wet Milling:

After Completion of the Drying, the composite samples were collected for corner of the tray dryer. Loss on drying for the sample was carried out on IR Moisture Balance. All three batches had LOD within 1-3 % which in the limit. Hence, drying process was validated for all batches.

Validation of Shifting and Sizing Process:

After completion of the drying passed the dried granules through 20# SS sieve on Sifter and reduce oversize by passing through 8 mm screen on multi mill. No damage was observed before and after passing dried granules through vibro shifter and multi mill of all batches. Hence, Shifting and Milling process was validated.

Validation of compression process:

During compression stage the average weight, individual weight, thickness, diameter,Hardness,friability, disintegration time, dissolution time of all batches were found within Specification. Hence, Compression stage for all batches was validated.

CONCLUSION:

The Prospective Validation of Loratadine Uncoated tablet has been performed for three batches (Batch A, Batch B, Batch C). The Validation data obtained shows they are within limits of their acceptance criteria as given in Validation protocol.

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