International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-2, 2015 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Process Validation of Ibuprofen Film Coated Tablets

Dukandar AD*[1], Tandel FB[1], Jha LL[1], Prajapati MP[2]

[1]*Department of Quality Assurance, Parul Institute of Pharmacy, Vadodara, Gujarat, India.*

[2]*Department of Quality Assurance, Norris Medicines Ltd., Ankleshwar, Gujarat, India.*

Manuscript No: IJPRS/V4/I2/00079, Received On: 29/04/2015, Accepted On: 08/05/2015

ABSTRACT

The main aim of the present research work was to study prospective process validation of Ibuprofen film coated tablet. If each step of production process is validated we can assure that the final product is of the best quality. Validation is best viewed as an impartment and integral part of cGMP. Validation is therefore one element of quality assurance programs associated with a particular process. Quality cannot be assured only by doing finished product testing and in-process monitoring but it should be built into the manufacturing process. So building of quality require a special attention to a few factors like selection of material, process design, control variables, in process control and finished product testing. In this study three initial batch of Ibuprofen tablet with same size, method, equipment and validation criteria were taken. The critical parameters involved in sifting, dry mixing, preparation of granulating agent, wet mixing, wet milling, drying, sizing, lubrication, compression stages and coating were identified and evaluated as per validation master plan. Results obtained with this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes. It also provides documented evidence for the operation sequence of manufacturing process and to determine the critical parameters and variables in the process of manufacturing of the tablets. The output of process validation can be used to increase productivity, its consistent quality and decreasing the need for processing or market complaints.

KEYWORDS

Ibuprofen, Tablets, Process Validation, Validation Protocol, Control Variables

INTRODUCTION

The aim of the research is to validate the process of manufacturing of Ibuprofen film coated tablet BP at the manufacturing plant of Norris Medicines Ltd., Ankleshwar. The objectives are to establish documented evidence that the process would consistently produce the product Ibuprofen film coated tablet BP, meeting its predetermined specifications by examining three consecutive production batches, to identify critical process parameters, to understand process and make it more precise and accurate by evaluating it, to understand sampling and testing plan and procedure, to prepare the validation protocol, to carry out prospective process validation and to prepare validation report.

Process validation is a systematic approach for identifying, measuring, evaluating, documenting and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product. As the dosage production involves numerous stages, it becomes very important to establish documented evidence that particular process has met pre-

***Address for Correspondence:**
DukandarAbdulaziz D.
Parul Institute of Pharmacy,
Vadodara- 391760, Gujarat, India.
E-Mail Id: dukandaraziz@gmail.com

determined specifications and quality characteristics. Quality is to be built in while manufacturing of the dosage form, end product testing is not enough. Therefore, Process validation is the way to confirm that the manufacturing process is validated. It reduces production cost, failures- rejections, reworks, complaints, product recalls and wastage of materials and increases output. In Norris Medicines Ltd., Ibuprofen film coated tablet BP 200 mg is a new product. Therefore, *prospective process validation* of Ibuprofen film coated tablet BP 200 mg was carried out.

Definition According to USFDA[1]

Process validation is establishing documented evidence that provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics.

Validation Principles[2]

The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. In order to meet this principle, a good understanding of the processes and their performance is important. Quality cannot be adequately assured by in-process and finished product inspection and testing but it should be built into the manufacturing processes. These processes should be controlled in order that the finished product meets all quality specifications. Process validation is intended to establish that the proposed manufacturing process is a suitable one and yields consistently a product of the desired quality. i.e. that the process is suitable and under control.

Importance of Validation[3]

1. Reduction of Quality Cost

Through proper validation, the cost of the following process can be optimized.

a) Preventive costs are costs incurred in order to prevent failures and reduce appraisal costs

b) Appraisal costs of inspection, testing and quality evaluation.

c) Internal failure costs

d) External failure costs that associated with a non-conformance condition after the product has left the company's ownership.

2. Process Optimization

The optimization of the facility, equipment system and closures etc. results in a product that meets quality requirements at the lowest costs. Trained, qualified people are the key elements in process optimization that results in improving efficiency and productivity.

3. Assurance of Quality

Validation and process control are the heart of GMPs. Without Validated and controlled process it is impossible to achieve quality products. Hence validation is a key element in assuring the quality of the product.

4. Safety

Validation can also result in increased operator safety. Properly calibrated, validated instruments and gauges used to reduce accident and results in safety.

5. Better Customer Quality

Through Proper validation, Market recall is avoided which result in better customer care and quality of the product.

Phases of Process Validation[4]

Phase 1: Pre-Validation Phase or the Qualification Phase, which covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, Equipment Qualification, master production documents, Process Capability.

Phase 2: Process Validation Phase (Process Qualification phase) designed to verify that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under the "worst case" conditions.

Phase 3: Validation Maintenance Phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including Change Control procedures.

Types of Process Validation[5]

1. Prospective validation
2. Concurrent validation
3. Retrospective validation
4. Revalidation

Validation Protocol[6]

A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment and design points on what constitutes acceptable test results.

The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information: Objectives, scope of coverage of the validation study, validation team membership, their qualifications and responsibilities, type of validation: prospective, concurrent, retrospective, revalidation, number and selection of batches to be on the validation study, a list of all equipment to be used.

Their normal and worst case operating parameters, outcome of IQ, OQ for critical equipment, requirements for calibration of all measuring devices, critical process parameters and their respective tolerances, description of the processing steps: copy of the master documents for the product, sampling points, stages of sampling, methods of sampling, sampling plans, statistical tools to be used in the analysis of data, training requirements for the processing operators, validated test methods to be used in in-process testing and for the finished product, specifications for raw and packaging materials and test methods, forms and charts to be used for documenting results, format for presentation of results, documenting conclusions and for approval of study results.

Validation Life Cycle[7]

Validation is a continuing and evolving process. The validation process extends from the very basic to a very broad theological and methodical investigation. Its scope encompasses documentation, revision control, training and maintenance of the system and process.

MATERIAL AND METHODS

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

Materials

Ibuprofen, lactose, maize starch, cross carmellose sodium, sodium methyl paraben, sodium propyl paraben, magnesium stearate, talcum powder, colloidal silicone dioxide, stearic acid, spraycel sc-3107 for film coating, isopropyl alcohol, methylene dichloride

Equipments and Instruments

Vibratory sifter with 20# and 40# sieves, paste preparation kettle, high shear rapid mixer granulator, multi mill equipped with 1.5 mm screen, fluid bed dryer system, octagonal blender, weighing balance, double rotary tablet compression machine with punches, dedusting unit, conventional metal detector, coating pan, blister packing machine, moisture analyser, weighing balance, Vernier caliper, tablet hardness tester (dial type), digital friability tester, disintegration test apparatus, HPLC, UV-Visible spectrophotometer

Table 1: Product Information Details

Name of Product	Ibuprofen Tablets 200 mg
Generic Name	Ibuprofen Tablets 200 mg

Label Claim	Each Film Coated Tablet Contains: Ibuprofen BP…….200 mg Excipients……q.s.
Description	Red Colored Round Biconvex Shaped Plain Film Coated Tablet
Effective Date	Jan – 2015
Batch Size	5,15,000 Tablets
Shelf Life	36 Months
Storage Condition	Store in a Cool Dry Place Protected from Light

Methods

Validation Procedure

1. Three batches of 5,15,000 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

Ibuprofen is sifted using 20# SS Sieve while lactose, 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:

Sift Talcum powder, Colloidal silicone dioxide, Cross carmellose sodium and stearic acid through 40# sieve and collect in a poly bag. Then load the sifted materials 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/cm^2.
- Friability Test: NMT 1.0% w/w
- Average Weight of Tablet: 390.00 mg.
- Weight Variation: NMT ± 5% of Average Weight.

Coating

Take in SS vessel isopropyl alcohol and dissolve spraycel 3107 for film coating. Add and mix methylene dichloride. Sieve the core tablets through 0.25 inch SS sieve. Blow air to remove the adhered powder from tablets. Dry the tablets with blow of hot air. Load tablets in coating pan. Apply coating solution to tablets with continuous spray using peristaltic pump and spray gun and keeping minimum 2.5-3 kg/cm sq. pressure of compressed air. Dry the tablets at 55-60 ºC continuously using blow hot air. Apply all coating solution and maintain bed temp.

Packaging

Print batch no., mfg. date, exp. Date on aluminum foil by coding machine. Set rubber stereo. Set forming roller temp at 130-160 ºC and sealing temp at 140-210 ºC.

Pack the tablets in foil, blister of 10 tablets by blister pack machine. Pack 10 tablets in overprinted carton.

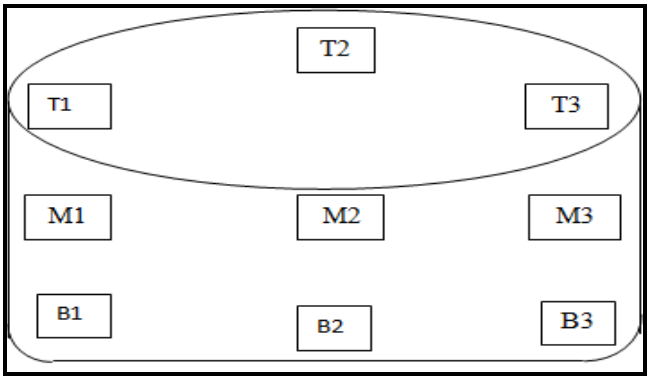

Figure 1: Sampling Diagram for Rapid Mixer Granulator

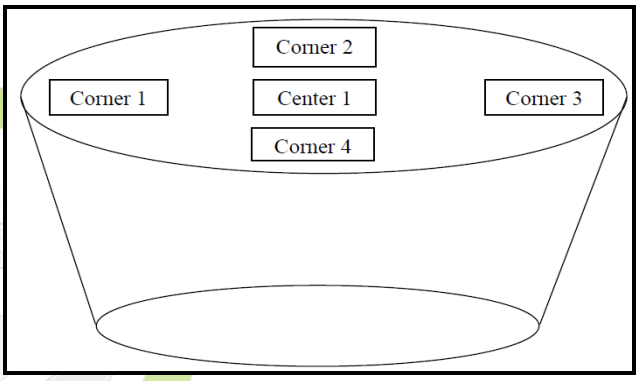

Figure 2: Sampling Diagram for Fluid Bed Dryer

Table 2: Sampling and Testing Plan

Stage	Sample Location	Sample Quantity	Test To Be Performed
Dry Mixing	3 Points from Top 3 Points from Bottom 3 Point from Middle of Bed from RMG	2 gm from Each Location	Blend Uniformity
At the End of Drying	From 4 Corner and 1 Center of FBD	5 gm from Each Location	LOD
Lubrication	3 Samples from Top, Bottom and Middle	2 gm	Blend Uniformity
	1 Composite Sample from 3 Different Locations using SS Sampling Rod	20 gm	Assay for Blend Uniformity
			Description
			% LOD
			Bulk Density
			Tapped Density
			Angle of Repose

Compression	Draw Tablets from Initial, Middle and Near to End Stage of the Compression	50 Tablets	Description
			Average Weight
			Weight Uniformity
			Thickness
			Diameter
	Draw Tablets as a Composite Sample from All Containers for Test Parameters	50 Tablets	Hardness
			Friability
			Disintegration Time
			Assay
Coating	Draw Tablets from Coating Pan at the end of each Lot	50 Tablets	Same as Previous Stage
Packaging	Draw Blisters at Initial, Middle and End of Packaging	10 Blisters	Appearance of Tablet
			Overprinting Quality

Critical Process Parameters

Table 3: Critical Process Parameters

Processing Stage	**Critical Process Parameter**	**Evaluation Test**
Sifting	Sieve Size	Sieve Integrity Before and After Use
	Sieve Integrity	
Dry Mixing	Mixing Time	Content Uniformity
	Mixing Speed	
Granulation	Binding Time	Check the Mixing Time
	Mixing Speed	
	Load Size	Ampere (End Point)
	Amount of Granulating Agent	
Drying	Total Drying Time	LOD
	Inlet and Outlet Temperature	
	Load Size	
Sifting and Milling	Sieve Size	Sieve Integrity
	Screen Type	
	Speed	
	Knives Direction	
	Feed Rate	
		Sieve Analysis

Lubrication	Mixing Time	Description
		Assay for Blend Uniformity
		LOD
	Blender Speed	Bulk and Tapped Density
		Sieve Analysis
Compression	Compression Speed	Appearance
		Average Weight. and Uniformity of Weight
		Thickness and Diameter
	Compression Force	Hardness and Friability
		Disintegration Time
	Granule Feed Rate	
		Assay
Coating	Spray Rate	Coating Weight
	Inlet and Outlet Temperature	
	Air Pressure	
	Speed of Rotation of Coating Pan	
Packaging	Forming and Sealing Temperature	Appearance of Tablet
		Sealing Quality (Knurling)
		Overprinting Quality
		Label Quality
		Leak Test

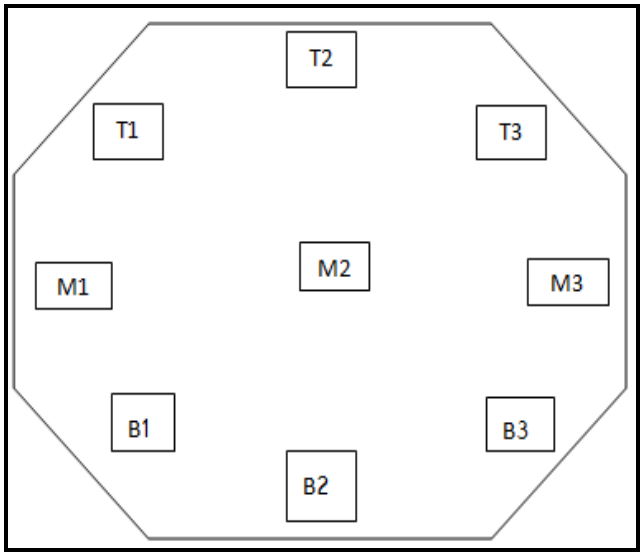

Figure 3: Sampling Diagram for Octagonal Blender

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 Ibuprofen 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 4: % Assay after 10 min Mixing

Value	Mixing time			Acceptance Criteria
	5 min	10 min	15 min	
% Assay (average)	97.99	99.95	97.75	95.0 % - 105.0 % of Labelled Amount
SD	0.52	0.65	0.85	
% RSD	0.53	0.65	0.87	NMT 3 %

Table 5: % LOD after Drying

Sample Location	% LOD			Standard
	Batch-A	Batch-B	Batch-C	
Left	0.90	1.11	1.21	NMT 2.0 % w/w
Right	0.73	0.92	0.99	
Center	1.14	0.85	1.35	
Front	1.00	0.76	1.13	
Back	0.87	1.28	0.86	

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 Ibuprofen tablets for all three validation batches were found within the limit of acceptance criteria. So dry mixing was performed for 10 min for routine manufacturing batches.

Wet Mixing

Temperature and relative humidity of room were27 ºC and 54 % respectively.

Binder solution preparation

Sufficient quantity of water was added and mixed slowly.

Addition of binder solution

Speed(Impeller: Slow, Chopper: Off) of RMG was slow. Binder addition time was 2 min. Mixing time (Impeller: Slow, Chopper: Slow) was 2 min. Mixing time (Impeller: Fast, Chopper: Fast) was 1 min. Total granulation time was 5 min and current drawn by impeller and chopper at granulation end point was 33 Amp.

Wet Milling

Impact of knife was forward at medium speed.

Integrity of Screen Before and After Use

8 mm screen was used. No damage & choking of screen were observed. Material was easily passed through screen.

Drying

Inlet and outlet temperature were 51 ºC and 42 ºC respectively. Total time of drying was 70 min.

% LOD was found NMT 2.0% w/w, which is within acceptance criteria. Drying was found to be homogeneous and efficient throughout the sample. Hence there are least chances of tablet defects like sticking due to insufficient drying and capping, lamination, cracking and chipping due to excessive drying.

Sifting

20# sieve was used. No damage of sieve was observed. No foreign particles were observed. Integrity of the sieve before and after was found intact.

Milling

Impact of knifewas forward at medium speed and 1.5 mm screen was used. No damage and choking of sieve were observed. Material was easily passed through screen. All the parameters during milling were found satisfactory and were within limit of specification.

Lubrication

Temperature and relative humidity were 27 ºC and 54 % respectively. Direction of knives was clockwise at 10 rpm speed. Lubrication Time was 30 min.

Composite Sample

All the results of composite sample for physical parameters were found within the acceptance criteria. Significant observation related to the flow of the blend was observed throughout the compression activity. Assay of composite blend for three batches was within the specification.

Compression

Temperature and relative humidity were 27 ºC and 54 % respectively. Turret Speed was24 rpm. Compression Force was 20 KN. Upper and lower punches were 12/32 std. concave plain.

Table 6: % Assay after Lubrication

Sr. No.	Sample Location	% Assay			Acceptance Criteria
		Batch-A	Batch-B	Batch-C	
1	T1	100.26	99.72	97.58	95.0 % - 105.0 % of Labelled Amount
2	T2	99.53	100.35	99.72	
3	T3	100.19	99.64	100.3	
4	M1	101.07	100.26	98.47	
5	M2	98.34	99.42	98.93	
6	M3	100.71	98.87	99.66	
7	B1	98.45	100.11	101.14	
8	B2	98.68	97.38	100.00	
9	B3	99.82	99.53	100.25	
10	**Min**	98.34	97.38	97.58	
11	**Max**	101.07	100.35	101.14	
12	**Mean**	99.67	99.48	99.56	
13	**SD**	0.10	0.91	1.08	
14	**% RSD**	0.10	0.92	1.08	NMT 3 %

It was evident that there was no segregation or demixing occurs in the blender and mixing is homogeneous throughout the sampling locations for all three batches at 30 min. % RSD of Ibuprofen tablets for all three validation batches were found within specification limit.

Table 7: Observation of Composite Sample after Lubrication

Test	Acceptance Criteria	Observation		
		Batch-A	**Batch-B**	**Batch-C**
Description	White to Off White Granule	Complies	Complies	Complies
% LOD	NMT 2.0 %	1.29	1.41	1.32
Assay %	95.0 % - 105.0 % of Labelled Amount	99.47	99.53	100.21
Bulk Density (gm/ml)	-	0.67	0.66	0.62
Tapped Density (gm/ml)	-	0.78	0.75	0.71
Angle of Repose	25-30	27.4	26.8	26.3

All the results of composite sample for physical parameters were found within the acceptance criteria. Significant observation related to the flow of the blend was observed throughout the compression activity. Assay of composite blend for three batches was within the specification.

Table 8: Observations for L.H.S. after Compression

Parameter	Acceptance Criteria	Observation						
			Batch-A		**Batch-B**		**Batch-C**	
Description	A White Colored Biconvex Plain Uncoated Tablet	Initial	Complies		Complies		Complies	
		Middle	Complies		Complies		Complies	
		End	Complies		Complies		Complies	
Weight of 20 Tablets (gm)	7.800 ± 2 % (7.644-7.956)	Initial	7.814		7.765		7.823	
		Middle	7.824		7.836		7.779	
		End	7.780		7.787		7.815	
Average Weight (mg)	390.0 ± 5% (370.5-409.5)	Initial	391.1		385.0		396.3	
		Middle	384.5		390.2		387.6	
		End	395.5		392.7		389.4	
Uniformity of Weight	± 5.0 % of Average Weight	%	Min	Max	Min	Max	Min	Max
		Initial	-2.1	+2.8	-2.9	+2.2	-3.5	+2.2
		Middle	-2.5	+3.7	-2.0	+2.7	-2.6	+2.4
		End	-3.6	+2.9	-3.8	+2.3	-2.4	+3.3

Thickness (mm)	5.3 ± 0.3 (5.0-5.6)	Initial	5.31	5.30	5.29
		Middle	5.34	5.28	5.32
		End	5.39	5.40	5.33
Diameter (mm)	10.0 ± 0.2 (9.8-10.2)	Initial	10.14	9.99	9.98
		Middle	9.98	10.03	10.11
		End	9.99	10.10	10.02
Hardness (kg/cm^2)	NLT 2.0	Initial	4.2	4.4	4.4
		Middle	4.5	4.0	4.3
		End	4.1	4.6	4.7
% Friability	NMT 1.0 %	Initial	0.12	0.16	0.19
		Middle	0.24	0.25	0.31
		End	0.17	0.23	0.28
Disintegration Time (min)	NMT 15’00”	Initial	3’10”	2’31”	2’53”
		Middle	2’46”	2’54”	3’22”
		End	3’07”	2’45”	2’38”
Assay %	95.0 - 105.0 % of Labelled Amount	Initial	97.92	99.33	100.16
		Middle	100.33	98.75	101.08
		End	99.61	100.24	98.87

Table 9: Observation of R.H.S. after Compression

Parameter	**Acceptance Criteria**	**Observation**			
			Batch-A	**Batch-B**	**Batch-C**
Description	A White Colored Biconvex Plain Uncoated Tablet	Initial	Complies	Complies	Complies
		Middle	Complies	Complies	Complies
		End	Complies	Complies	Complies
Weight of 20 Tablets (gm)	7.800 ± 2 % (7.644-7.956)	Initial	7.720	7.837	7.775
		Middle	7.814	7.766	7.829
		End	7.884	7.885	7.713
Average Weight (mg)	390.0 ± 5% (370.5-409.5)	Initial	397.5	384.0	391.6
		Middle	383.1	390.7	388.3
		End	394.5	391.2	389.4

Uniformity of Weight	± 5.0 % of Average Weight	%	Min	Max	Min	Max	Min	Max
		Initial	-2.8	+2.4	-2.6	+2.8	-3.1	+3.2
		Middle	-2.6	+3.8	-3.0	+3.0	-2.9	+2.6
		End	-2.2	+2.9	-2.8	+2.7	-2.9	+2.5
Thickness (mm)	5.3 ± 0.3 (5.0-5.6)	Initial	5.20		5.21		5.37	
		Middle	5.39		5.38		5.36	
		End	5.34		5.32		5.40	
Diameter (mm)	10.0 ± 0.2 (9.8-10.2)	Initial	10.13		10.11		9.98	
		Middle	10.02		9.97		10.03	
		End	9.98		10.14		9.99	
Hardness (kg/cm^2)	NLT 2.0	Initial	4.1		4.5		4.4	
		Middle	4.3		4.6		4.7	
		End	4.2		4.0		4.5	
% Friability	NMT 1.0 %	Initial	0.28		0.24		0.26	
		Middle	0.15		0.17		0.32	
		End	0.29		0.33		0.11	
Disintegration Time (min)	NMT 15’00”	Initial	2’46”		2’43”		3’14”	
		Middle	2’38”		2’35”		2’47”	
		End	2’16”		3’19”		3’25”	
Assay %	95.0 - 105.0 % of Labelled Amount	Initial	101.07		100.26		99.32	
		Middle	98.78		98.83		97.91	
		End	100.14		99.65		100.33	

Table 10: Observation of Composite Sample after Compression

Parameter	**Acceptance Criteria**		**Observation**		
			Batch-A	**Batch-B**	**Batch-C**
Description	A White Colored Biconvex Plain Uncoated Tablet		Complies	Complies	Complies
Weight of 20 Tablets (gm)	7.800 ± 2 % (7.644-7.956)		7.834	7.787	7.891
Average Weight (mg)	390.0 ± 5% (370.5-409.5)		390.6	390.5	391.2
Uniformity of Weight	± 5.0 % of Average Weight		Complies	Complies	Complies
% Friability	NMT 1.0 %		0.21	0.19	0.23
Disintegration Time (min)	NMT 15		3’24”	3’13”	2’56”
Assay %	95.0 - 105.0 % of Labelled Amount		99.86	100.13	99.72
Thickness (mm)	5.3 ± 0.3 (5.0-5.6)	Min	5.12	5.18	5.21
		Max	5.44	5.43	5.56
		Avg	5.20	5.37	5.35
Diameter (mm)	10.0 ± 0.2 (9.8-10.2)	Min	9.94	9.92	9.95
		Max	10.14	10.11	10.13
		Avg	9.99	10.03	10.05
Hardness (kg/cm^2)	NLT 2.0	Min	3.9	3.9	3.8
		Max	5.7	5.4	5.6
		Avg	4.8	4.5	4.2

Compression process was carried out as per instruction given in BMR. The results of all parameters for L.H.S., R.H.S. and composite sample were found within the acceptance criteria.

Coating

Air Pressure was 2.6 kg/cm^2. Inlet Temperature and outlet temperature were 57 ºC and 46 ºC respectively. Pan was rotated at 10 rpm.

Blister Packing

Forming and sealing roller temperature were 150 ºC and 179 ºC.

Cutting was proper. No knurling was observed.

Sealing of the finished pack was proper. Overprinting details were observed as per requirement. Leak Test was passed. As per the online recorded data during the packing stage, all the parameters for all three batches were within the specification.

Finished Product Tests and Observation

Table 11: Finished Product Tests and Observation

Test Parameter	Standard	Observation		
		Batch-A	Batch-B	Batch-C
Description	Red Colored Round Shaped Biconvex Plain Film Coated Tablet	Complies	Complies	Complies
Identification	A. The Infrared Absorption Spectrum is concordant with the Reference Spectrum of Ibuprofen B. Melting Point about 75 ºC	Complies	Complies	Complies
Average Weight (mg)	400.0 ± 5 % (380.0-420.0)	398.0	404.0	401.0
Uniformity of Weight	± 5.0 % of Average Weight	Complies	Complies	Complies
Thickness (mm)	5.4 ± 0.3 (5.1-5.7)	5.48	5.52	5.45
Diameter (mm)	10.1 ± 0.2 (9.9-10.3)	10.14	10.11	10.16
Hardness (kg/cm^2)	NLT 3.0	5.3	5.0	4.9
Disintegration Time (min)	NMT 30.0	9’32”	9’24”	8’51”
% Assay	95.0 % - 105.0 % of Labelled Amount	99.94	100.73	100.85

The results of all tests were found within the acceptance criteria.

Process Capability Analysis

1. Process capability and sixpack report for % assay after dry mixing

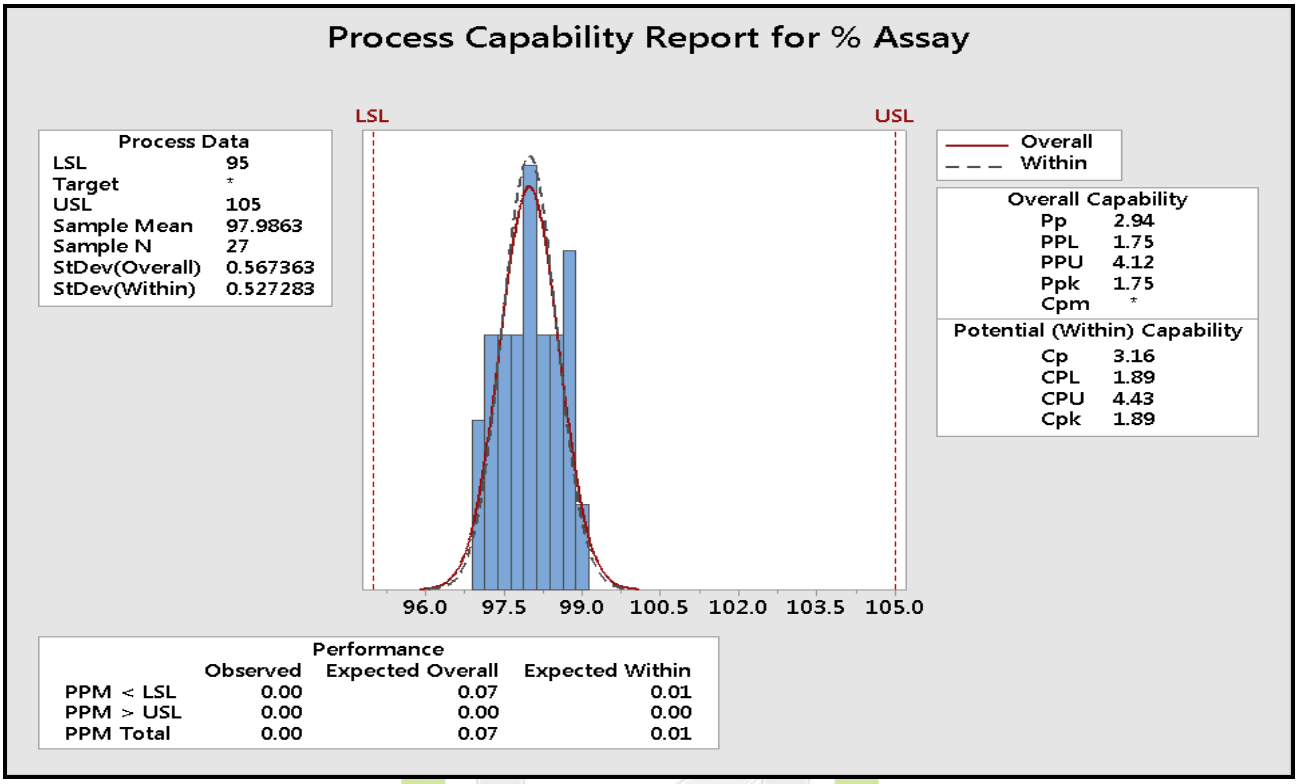

Figure 4: Process Capability Report for % Assay after Dry Mixing

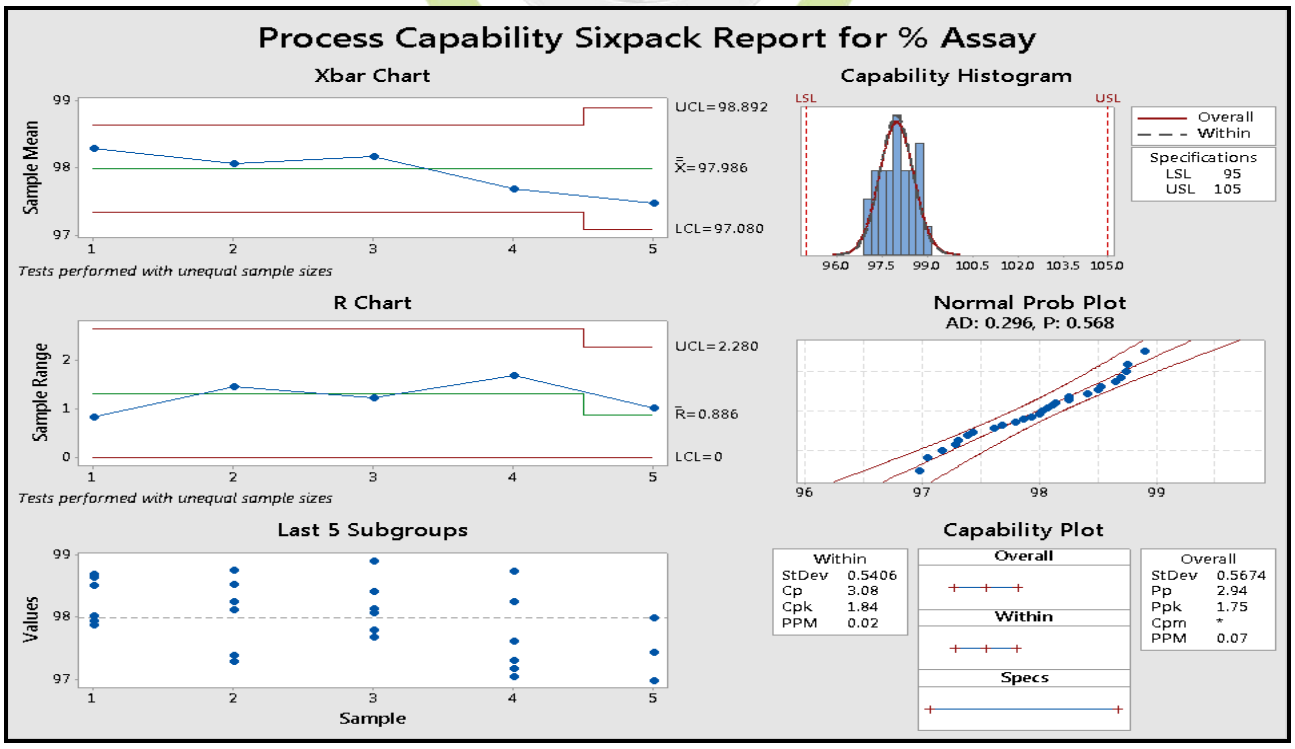

Figure 5: Process Capability Sixpack Report for % Assay after Dry Mixing

2. Process capability and sixpack report for % LOD after drying

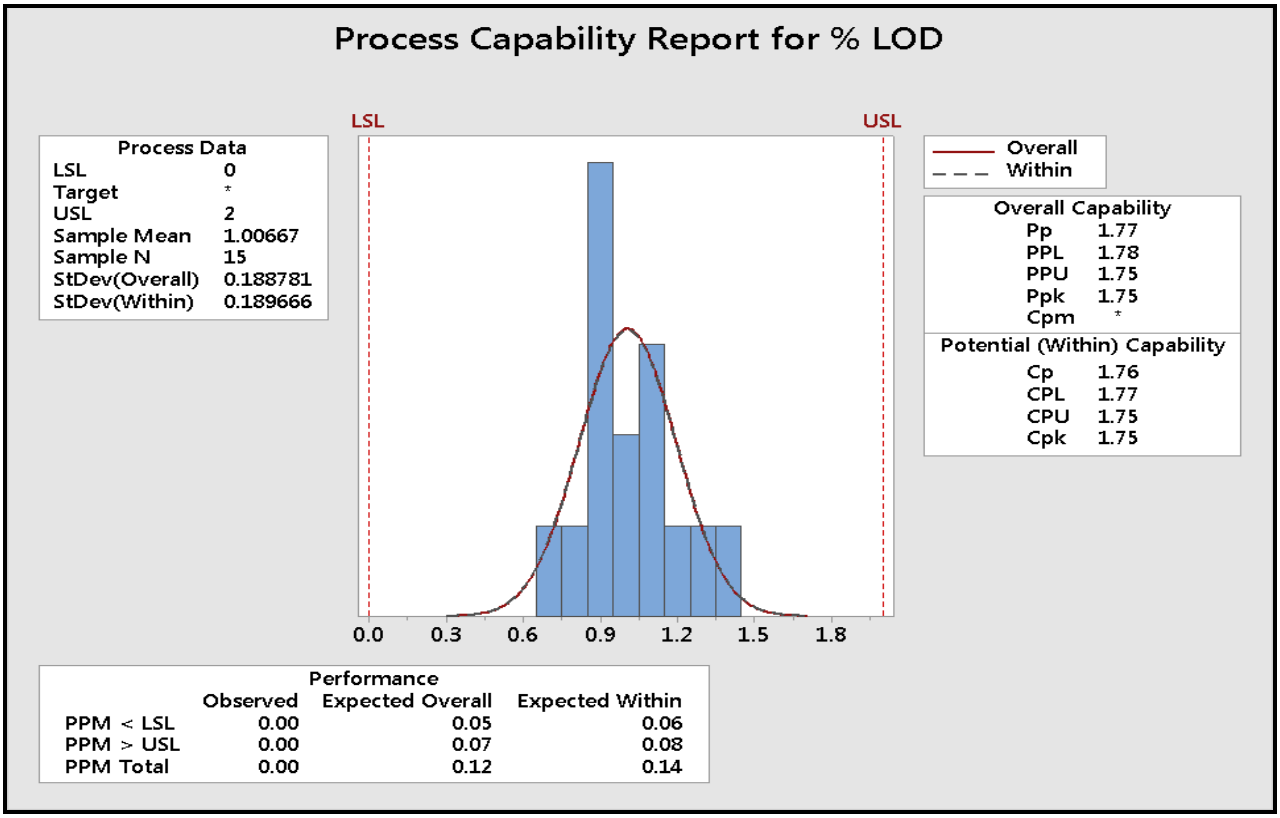

Figure 6: Process Capability Report for % LOD after Drying

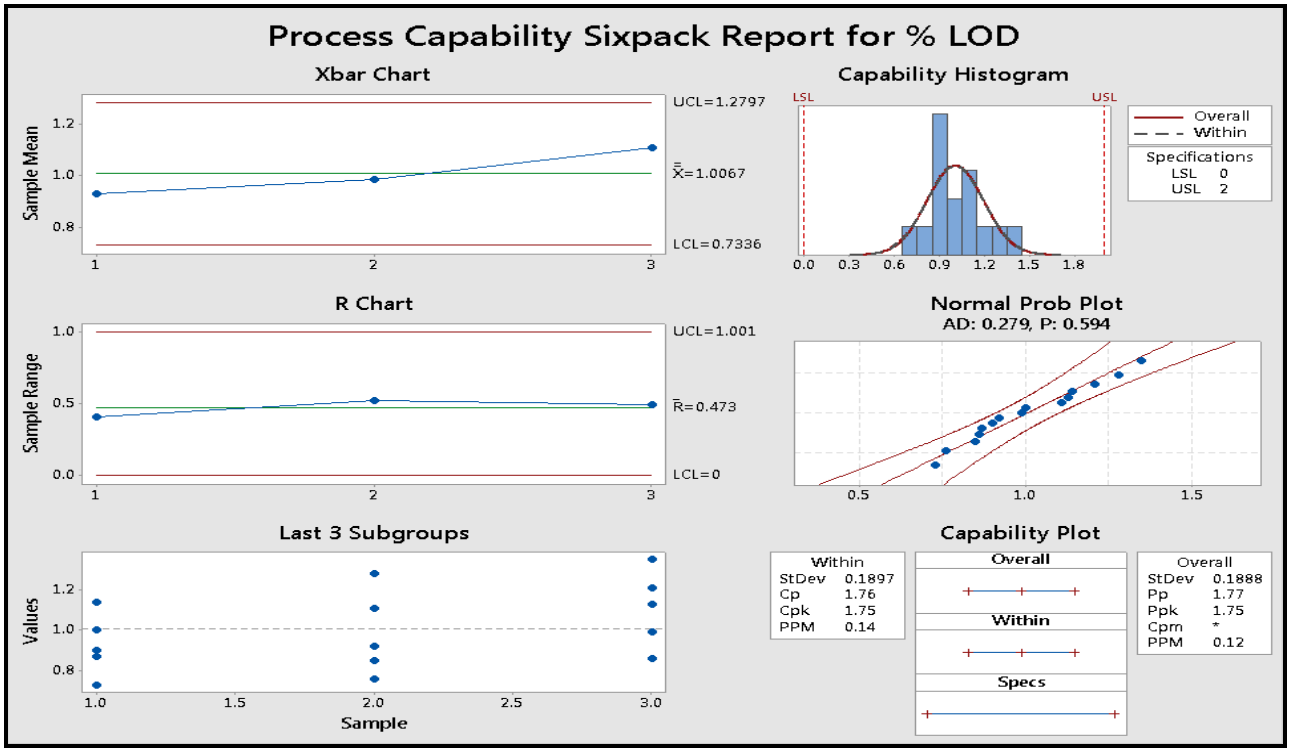

Figure 7: Process Capability SixpackReport for % LOD after Drying

3. Process capability and sixpack report for % assay after lubrication

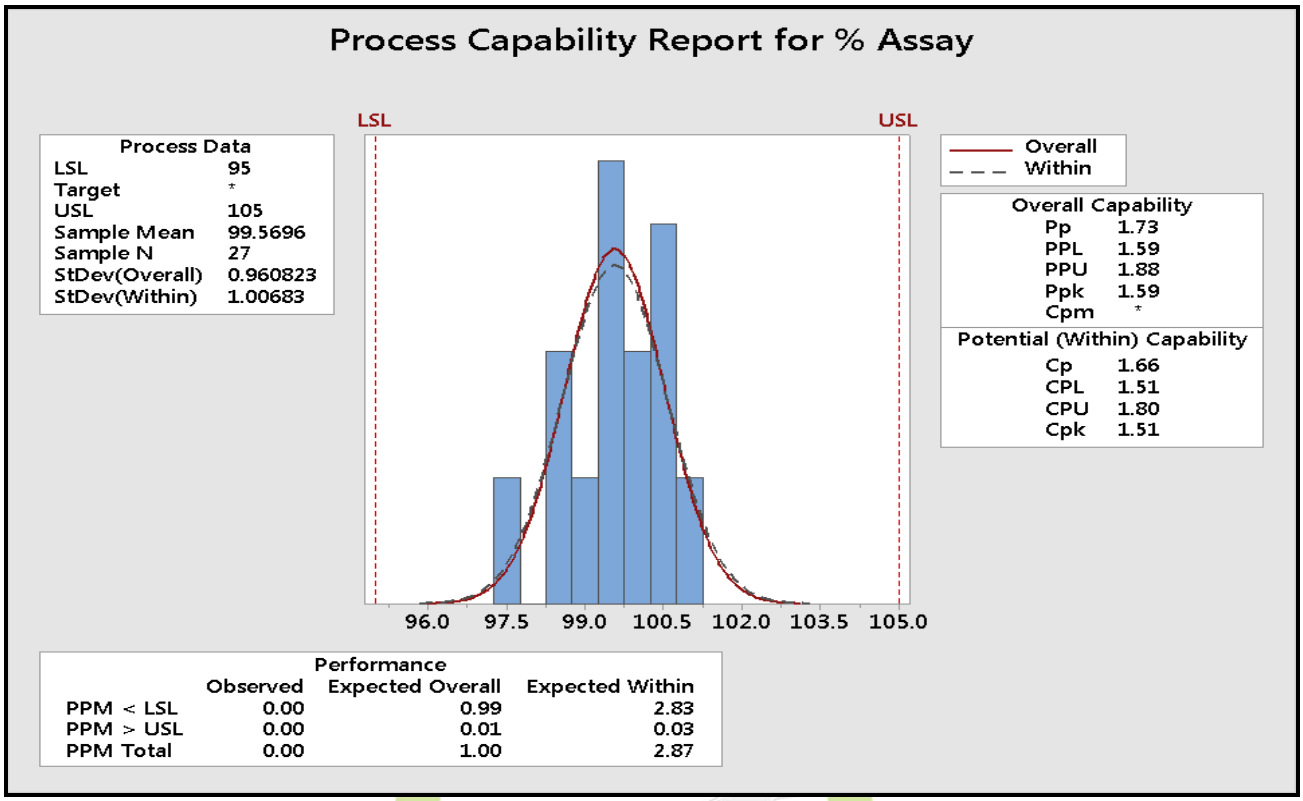

Figure 8: Process Capability Report for % Assay after Lubrication

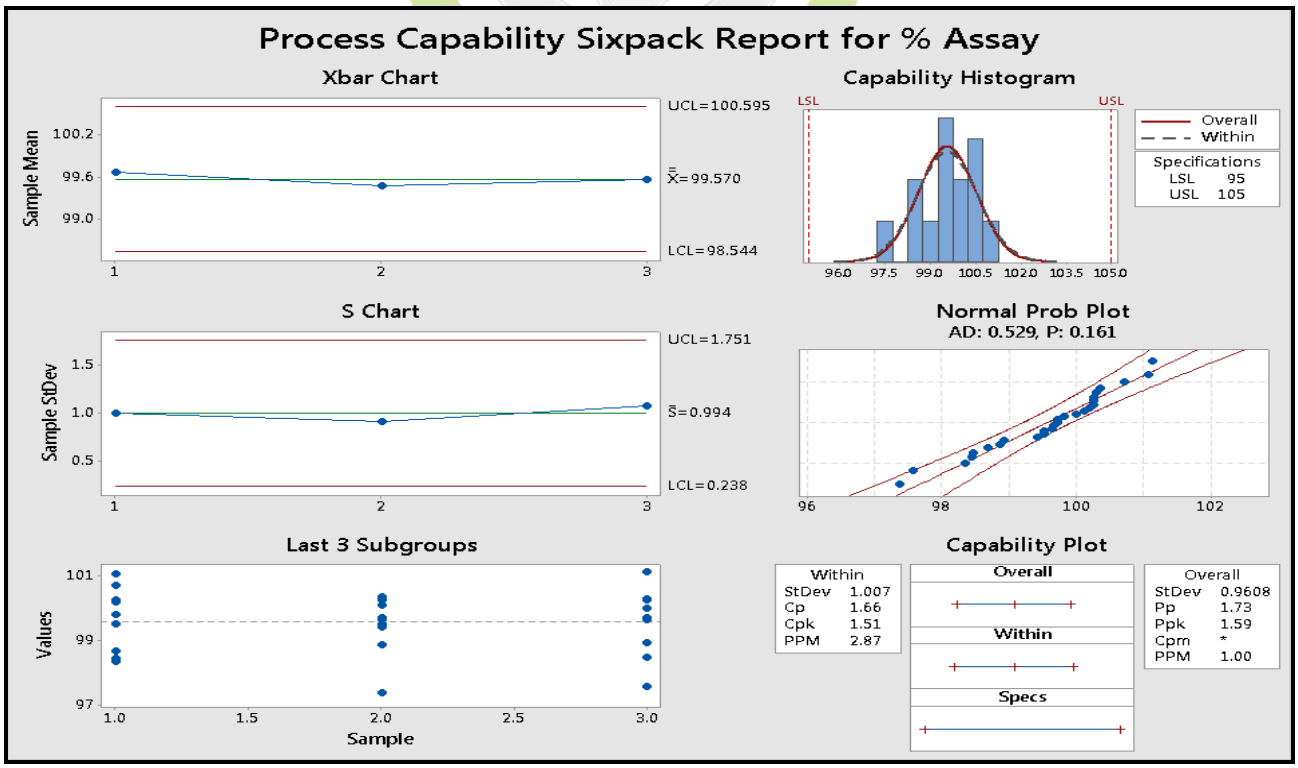

Figure 9: Process Capability Sixpack Report for % Assay after Lubrication

4. Process capability and sixpack report for weight variation after compression

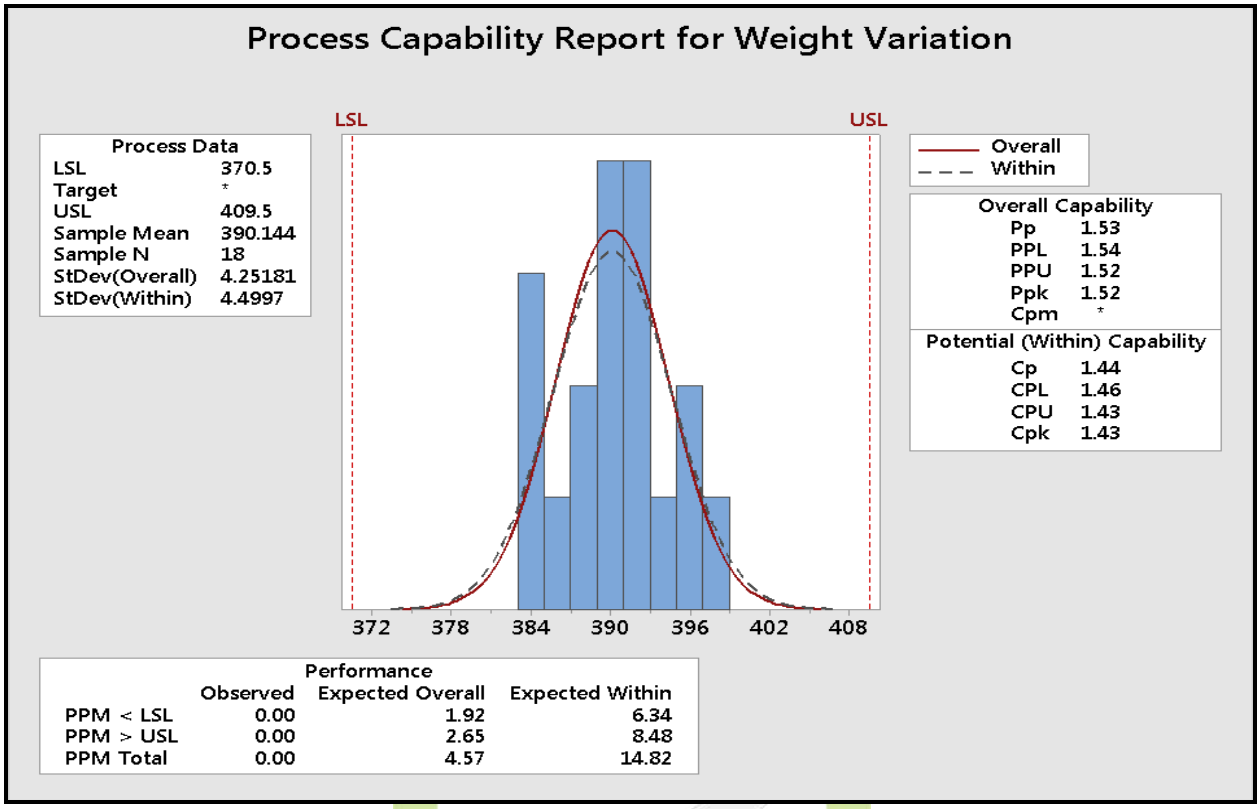

Figure 10: Process Capability Report for Weight Variation after Compression

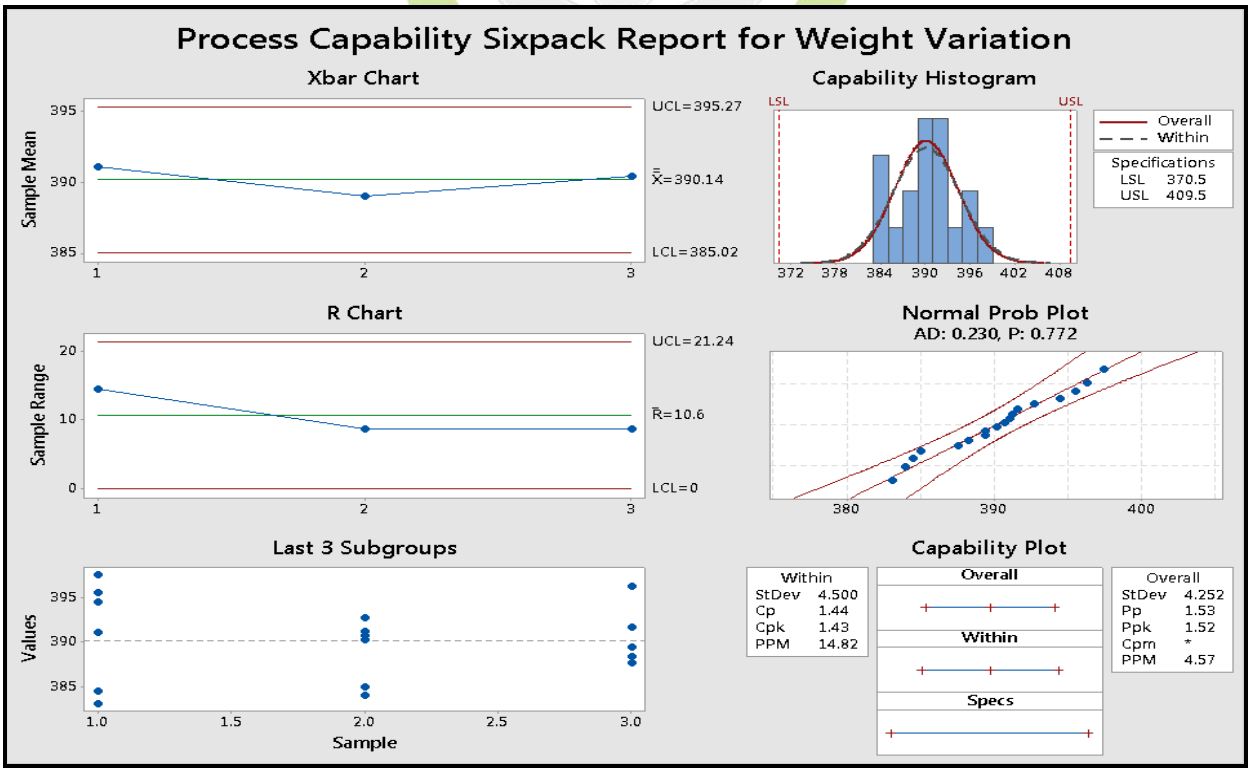

Figure 11: Process Capability SixpackReport for Weight Variation after Compression

Results of Capability Indices

Table 12: Capability Indices Results

Capabi-lity Indices	% Assay (DM)	% LOD	% Assay (L)	Wt. Variation
Cpk value	1.89	1.75	1.51	1.43
X bar	97.99	1.01	99.57	390.14
Defects PPM value	0.07	0.12	1.00	4.57

Interpretation

Table 13: Value of Cpk Related to Process Capability

Cpk < 1	Poor process
Cpk = 1.0	So ok
Cpk 1.3- 1.5	Good
Cpk = 2	Excellent that is six sigma

Table 14: Defect Parts Per Million Related to the Sigma Level

Sigma level	Defect per million opportunities (PPM)
2	308,537
3	66,807
4	6,210
5	233
6	3.4

Table 15: Cpk Value and Their Equivalent Parts Per Million (PPM)

Cpk	Defects Parts Per Million Opportunities
0.50	66800
0.62	65000
0.68	40000
0.75	25000
0.81	15000
0.86	10000
0.91	6500
1.00	1350

- Defects parts per million (PPM) for blend uniformity, LOD, % assay and weight variation of tablets were found to be 0.0, 0.1, 1.0 and 4.6 respectively. So that all the parameters meet the specifications under four to six sigma levels. From the above statistical analysis, it was concluded that the process was capable to meet its predetermined specifications.
- The Cpk values for all parameters were found more than 1. It means that all process parameters complies the specifications criteria and process was capable to produce product meeting its predetermined specifications. Xbar values of studied parameters for all the three batches shows that mean value fall within the limit/acceptance criteria for all the parameters.

CONCLUSION

It can be concluded that the observations and results that each unit process involved in the manufacturing of Ibuprofen tablet were efficient enough and capable of producing the desired tablets consistently and uniformly. Dry mixing,

wet mixing, drying, lubrication and compression in-process parameters were found acceptable for all the three batches. No parameter was deviating outside the range of acceptance criteria.

It is concluded that the manufacturing process for the Ibuprofen tablets was efficient enough to provide a high degree of assurance that it would produce the tablets consistently and uniformly with acceptable and uniform results.

ACKNOWLEDGEMENT

The author is thankful to Norris Medicines Ltd., Ankleshwar for giving the opportunity and providing necessary facilities to carry out this work.

REFERENCES

1. Thaduvai, R., Rao, B. S., & Jeybaskaran, M. (2012). Process Validation of Pantoprazole 40 mg Tablets. *The Pharma Innovation*, 1(5), 47-62.
2. Patel, V. B., Rathwa, M. R., & Patel, K. (2011). Studies in Prospective Process Validation of Cimetidine Tablet Dosage Form. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2(4), 1823-1836.
3. Patel, H. P., Shrivastava, A. K., & Jindal, D. (2012). Process Validation of Benazepril HCl 5 mg Tablet. *International Research Journal of Pharmaceutical and Applied Sciences*, 2(4), 1-16.
4. Paruchuri, R., Trivedi, S., Pavuluri, G., B, P., & M, S. K. (2012). Process Validation of Finasteride Tablets. *International Journal of Pharmaceutical, Chemical and Biological Sciences*, 2(1), 11-28.
5. Salunke, S. P., Shirole, R. L., Wagh, R. D., &Shirole, N. L. (2014). Concurrent Process Validation of Magnesium Hydroxide & Aluminum Hydroxide as Chewable Tablet. *World Journal of Pharmacy and Pharmaceutical Sciences*, 3(10), 1743-1766.
6. Patel, N., Vaghasiya, J., Patel, P., & Panchal, K. (2013). Process Validation of Nifedipine Film Coated Tablet. *Pharmagene*, 1(2), 25-31.
7. Patel, A. K., Vekariya, C. N., Chauhan, R. S., & Shah, S. A. (2013). Process Validation of Cefuroxime Axetil Film Coated Tablets. *International Journal for Pharmaceutical Research Scholars*, 2(2), 79-92.

