IJMPR 2019, 3(3), 11-26

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 3.458

PROCESS VALIDATION OF MANUFACTURING OF SOLID DOSAGE FORM USING PANTOPRAZOLE SODIUM TABLETS

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Received on: 30/03/2019
Revised on: 20/04/2019
Accepted on: 10//05/2019

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ABSTRACT

Introduction: Validation is most important Part of cGMP, which require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. The validation study provides the accuracy, sensitivity, specificity, and reproducibility of the test methods. **Method:** Process validation of pantoprazole 40mg tablets is conducted, which included the validation of critical steps of manufacturing such as blending, compression and coating. **Result & Conclusion:** Validation of Pantoprazole-40 Tablet is subjected to physicochemical studies using parameter such as Thickness, Diameter, Hardness, Weight variation, Content uniformity, Disintegration, Dissolution. For all these parameter, average Values and variation are within the limits at each stage of testing.

KEYWORDS: cGMP, Validation, Dissolution, Disintegration, Content Uniformity, Weight Variation etc.

1. INTRODUCTION

Validation is a concept that has evolved in United States in 1978. It is an important and integral part of cGMP. The word validation simply means assessment of validity or action of proving effectiveness. Validation is a team effort where it involves people from various disciplines of the plant. 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 each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.[1]

1.1 Importance of Validation.[2,3]

- Assurance of quality
- Time bound
- Process optimization
- Reduction of quality cost
- Minimal batch failures, improved efficiently
- Reduction in rejections
- Increased output
- Reduced testing in process and in finished goods
- More rapid and reliable start-up of new equipment
- Easier scale-up form development work
- Improved employee awareness of processes
- More rapid automation
- Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products)

2. MATERIAL AND METHOD

2.1Manufacturing Formula[4]

Table 1: Manufacturing Formula.

S. No.	Ingredient	Spec.	Label claim	Amount Per unit(mg)	Overages(%)	Weight/ tablet after overages	Std. Qty.(kg)
A	**DRY MIXING**						
01	Pantaprazole sodium	*IP	40	45.111	3	46.464	92.928@
02	Sodium carbonate anhydrous	*IP	-	-	-	10.000	20.000
03	Mannitol	*IP	-	-	-	39.036	78.072@
04	Crospovidone	*IP	-	-	-	27.000	54.000
B)	**BINDER**						
05	Povidone (k-30)	*IP	-	-	-	4.000	8.000
C)	**Lubrication**						
06	Crospovidone	*IP	-	-	-	8.000	16.000
07	Calicium stearate	*IP	-	-	-	3.000	6.000
08	Talc	*IP	-	-	-	2.500	5.00
	Total weight		-	-	-	**140.000**	**280.000**
	Coating material						
A)	**Base coating**						
09	Colouropadry (white OY-C-7000A)	*IP	-	2.5000	20#	3.000	6.000
10	IPA	*IP	-	13.000	-	13.000#	26.000#
11	Dichloro-methane	**BP	-	19.5000	-	19.500#	39.000#
B)	**Enteric Coating**						
12	Colour Acryl EZE Yellow 93O52098	*IP	-	16.500	10#	18.150	36.300
	Total weight	**(after coating)**	**-**	**159.000**	**-**	**-**	**318.000**

***IP- Indain pharmacopeia**

****BP- British pharmacopeia**

@ Quantity shall be calculated based on assay (on dried basis) and water

@@ Quantity of Mannitol IP shall be compensated for potency calculation with pantoprazole to maintain the average weight of a tablet.

Overage not included in total weight

Actual amount of pantoprazole sodium by calculating with molecular weight

Amount of pantoprazole sodium= Molecular wt.ofpantaprazole × label claim Molecular wt.ofpantaprazole

Actual amount of pantoprazole sodium= 432.356×40/383.37= 45.11 mg

2.2 Manufacturer of Raw Material[5]

Table 2: Lists of Manufacturer of Excipient.

S. No.	Ingredients	SPEC.	Manufacturer
1.	Pantaprazole sodium	IP	1. M/S Vasudhapharmachem Ltd. Vishakhapatnam-531020 2. Rakshit drugs PVT. LTD. Andhra Pradesh
2.	Sodium carbonate anhydrous	IP	1. M/S Thermofisher scientific, Sieon(E), Mumbai 2. M/S Qualigen fine chemicals, Mumbai 3. M/S RFCL LTD., New Dehli
3.	Mannitol	IP	1. RoquetteFreres 62136 Lestrem France 2. Qingdao Bright Moon Seaweed Group Co. Ltd. Qingdao, China
4.	Crospovidone	IP	1. ISP Chemical Ltd. Calvert City, Kentucky.
5.	Povidone (k-30)	IP	1. ISPChemicalLtd.CalvertCity, New Gersy 2. AshlandSpecialtyIngredientCalvertCity (USA).
6.	Calicium stearate	IP	1.M/S Parag Fine Organics Veoor Pal ghar. 2.M/S Sparchaem Labs. Parwanoo-173220
7.	Talc	IP	1.M/S Neelkanthmineschem A-282,IST phase, Jodhpur 2. M/S Neelkanthmineschem E-63, 1- phase, Jodhpur
8.	Colouropadry (white	IP	1. Colourcon Asia PVT. Ltd., M-18 verna ,Industrial estate, GOA

	OY-C-7000A)		
9.	IPA	IP	1. Lee Chang Yung Chemical Industries, Taiwan 2. Deepak fertilizer and petrochemicals, TalojaRaigarh
10.	Dichloro-methane	BP	1. M/S GujratAlkalies and Chemicals, Chennai. 2. M/S ChemplastSanmer Ltd. Vadodara.
11.	Colour Acryl EZE Yellow 93O52098	IP	1. Colourcon Asia PVT. Ltd., M-18 verna ,Industrial estate, GOA

2.3 List of Equipment Used In Manufacturing

Table 3: Shows Lists of Equipment.

S. No.	EQUIPMENT	MAKE	CAPACITY/DIMENSION
1.	Dispensing Booth-I	Air Fill Solution	NA
2.	Dispensing Booth-II	Air Fill Solution	NA
3.	Solvent Dispensing Booth	Air Fill Solution	NA
4.	Weighing balance	Essae	210 gm
5.	Weighing balance	Essae	15 kg
6.	Weighing balance	Essae	300 kg
7.	Sifter-I	Solace	30”
8.	Sifter-II	Solace	30”
9.	Paste Preparation Vessel	Sams	100 ltr.
10.	RMG	Solace	600 ltr,
11.	FBP	Solace	250 kg
12.	FBE	ACG	250 kg
13.	Multimill	PragatiEngg.	NA
14.	Square cone Blender	Solace	1200 ltr.
15.	Post Bin Blender	Solace	600 ltr.
16.	Compression –I	Solace	495000 tabs/hour
17.	Compression –II	Cadmach	324000 tabs/hour
18.	Compression –III	Cadmach	210000 tabs/hour
19.	Metal Detector	Unique	NA
20.	Deduster	Unique	NA
21.	Autocoater	Solace Engg.	60”
22.	Colloid Mill	Cemach	NA
23.	Stirrer	PPE	NA
24.	Solution Holding Tank	Solace	1580 ltr.
25.	Hardness tester	Labindia	NA
26.	Friability apparatus	Electrolab	NA
27.	VernierCalliper	Mitutoyo	Upto 200mm
28.	Disintegration apparatus	Electrolab Labindia	NA
29.	Halogen moisture analyzer	Effem Technology	NA

2.4 Process overview.[6]

Dispensing
↓
Sifting
↓
Granulation
↓
Drying and sizing
↓
Lubrication
↓
Compression
↓
In process checking, packing
↓
Final product analysis and release.

2.5 Rationale for Selection of Critical Steps and Its Process Parameters for Validation

2.5.1 Blending[7,8]

This step involves mixing of granules with other blending material. The purpose of blending is to get a uniform distribution of pantoprazole sodium .This is followed by mixing of the blend with calcium stearate (Lubrication to get good flow and anti-adhesion property of the blend). Mixing speed and time are critical variables in this process. Since speed of the blender is constant, proper mixing time shall be determined.

2.5.2 Compression

This step involves Conversions of blended material into tablets as per specifications. Speed of machine, tablet thickness and hopper level are the major variables. So,

following parameters are to be checked to establish the above-mentioned variables at regular intervals

A. Description
B. Weight variation (group and individual)
C. Hardness
D. Thickness
E. Friability
F. Disintegration time
G. Dissolution time
H. Content uniformity
I. Impurities

2.5.3 Coating

The coating is application of coating material to a moving bed of tablets with concurrent use of heated air & to facilitate evaporation of solvent.

2.6 Validation Procedure

1. Three batches of 60.00 Lacs 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 yield after blending, Compression, Coating and Inspection.

2.7 Manufacturing Instruction along with control parameter for Critical Process

2.7.1 Dispensing[9]

Ensure that environmental condition (Temp. and RH) in dispensing and manufacturing area are within the prescribed limit (Temp. 15-25˚C and RH NMT 60%).

Equipment: Weighing balance, RLAF

Raw material shall be dispensed in dispensing booth under LAF as per Formulation order. Prior to commencement for manufacturing, weighing and confirmation of raw material shall be received as per the formulation order.

2.7.2 Sifting

Equipment: Vibrosifter

Material shall be sifted according to below table and sifted material should be collected in a double polylined container.

Table 4: Shows Lists of Ingredients to be sieved.

S. No.	Ingredients	Sieve Mesh Size#
1.	Pantaprazole sodium IP	30#
2.	Sodium carbonate anhydrous IP	30#
3.	Mannitol IP	30#
4.	Crospovidone IP	30#
5.	Povidone (k-30) IP	60#
6.	Calicium stearate IP	60#
7.	Talc IP	60#

2.7.3Binder preparation

Equipment: S.S. container

Take Suitable Quantity of Purified Water in S.S container and add reqd. Quantity of Povidone K-30 IP and dissolve with Continuous Stirring till Translucent Binder is obtained.

2.7.4 Granulation

Granulation is carried out for various reasons, one of which is to prevent the segregation of the constituents of powder mix. Segregation is due to differences in the size or density of the component of the mix. Normally, the smaller and/or denser particles tend to concentrate at the base of the container with the larger and/or less dense ones on the top. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule and segregation of granules will not occur.

For example, if one were to make tablets from granulated sugar versus powdered sugar, powdered sugar would be difficult to compress into a tablet and granulated sugar would be easy to compress.

In the pharmaceutical industry, two types of granulation technologies are employed: wet granulation and dry granulation.

2.7.4.1 Wet granulation

In wet granulation, granules are formed by the addition of a granulation liquid onto a powder bed which is under the influence of an impeller (in a high-shear granulator), screws (in a twin screw granulator) or air (in a fluidized bed granulator). The agitation resulting in the system along with the wetting of the components within the formulation results in the aggregation of the primary powder particles to produce wet granules.[10,11]

2.7.4.2 Dry granulation

The dry granulation process is used to form granules without using a liquid solution because the product granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. In this process the primary powder particles are aggregated under high pressure. Sweying granulator or a roll compactor can be used for the dry granulation.[12,13]

When a tablet press is used for dry granulation, the powders may not possess enough natural flow to feed the product uniformly into the die cavity, resulting in varying degrees of densification. The roller compactor

(granulator-compactor) uses an auger-feed system that will consistently deliver powder uniformly between two pressure rollers. The powders are compacted into a ribbon or small pellets between these rollers and milled through a low-shear mill. When the product is compacted properly, then it can be passed through a mill and final blend before tablet compression.[15]

Equipment: FBE[17,18]

2.8 Parameters to be checked

2.8.1 Spray Rate Determination

Perform the spray test to select the spray pump RPM to attain the target spray rate 650 to 1300 g/min.

Charge the sifted Pantaprazole sodium IP, Sodium carbonate anhydrous IP, Crospovidone IP, Mannitol IP in FBE Bowl.Set the FBE with following Parameter and dry mix the material for 15 min.

2.8.2 DRY MIXING

Carry out the testing of physical parameters as mentioned in the below table

Table 5: Shows Lists of Parameter to checked.

Parameter	Standard limit
Inlet air temp.	0˚C - 70˚C
Exhaust air Temp.	0˚C - 50˚C
Product Temp.	0˚C - 50˚C
Drive	Auto
Air Flow	0-1200 CFM
Shaking Time	3-7 sec
Shaking Interval	30-150 sec
SFM Sensitivity	15-20%

2.8.3 Binder Addition

Carrying out Testing of Spraying the binder solution with following set parameter of FBE [19]

Table 6: Lists of Parameter to checked.

Parameter	Standard limit
Inlet air temp.	0˚C - 75˚C
Exhaust air Temp.	0˚C - 50˚C
Product Temp.	0˚C - 50˚C
Atomization Pressure	0.5 – 5.0 bar
Dew Point	7-15
Spray Rate	650-1300 g/min
Spray Pump RPM	40-80 RPM
Drive	Auto
Air Flow	0-1800 CFM
Shaking Time	3-7 sec
Shaking Interval	30-150 sec
SFM Sensitivity	15-20%

2.8.4 Drying

Carrying out Testing of Dry Granules with following parameters till LOD reaches within Limit (2.5 to 3.0%).[20]

Table 7: Lists of Parameter to checked.

Parameter	Standard limit
Inlet air temp.	0˚C - 75˚C
Exhaust air Temp.	0˚C - 60˚C
Product Temp.	0˚C - 60˚C
Drive	Auto
Exahust Flap	100%
Air Flow	0-1500 CFM
Shaking Time	3-7 sec
Shaking Interval	30-150 sec
SFM Sensitivity	15-20%

2.8.5 Sifting and Sizing

Equipment: Vibrosifter and Multimill

Dreid granule shall be passed through sifter by using 16# sieve.

Sifted granule shall be passed through by using 1.5mm screen and pass the oversized granules through 16#.

2.8.6 Blending[21]

Equipment: Square cone Blender

Transfer approx. half quantity of milled dry granules in square cone blemder.

Mix the crosspovidone and Talc in Polybag (900×610) for 5 min.. Divide the mixture into 8 equal parts.

Add 1 part of step 2 to 1 part of step 3. Mix thouroughly. Repeat this step for Remaining parts of step 2 and 3.

Load all geometrically mix parts to blender close the bin and check for the tightness.

Unload the 30 kg of blended granules and mix calcium stearate geometrically in unloaded granules.

Transfer it in blender and run the blender for 3 min. at 10 RPM.

Unload the Granules in IPC bin,Weigh and label and transfer to blend Quarantine.

2.8.7 Yeild of Blended Granules

Limit: 99.0 to 100.0% w/w

2.9 Sampling Procedure[22,23]

2.9.1Blending: Load sifted materials into the square cone Blender except Calcium stearate.Start the blender in inch mode and check for any leakage of material. On ensuring that there is no leakage, blend for 18 minutes.Samples to be drawn from 13 locations of the blender as shown in figure.

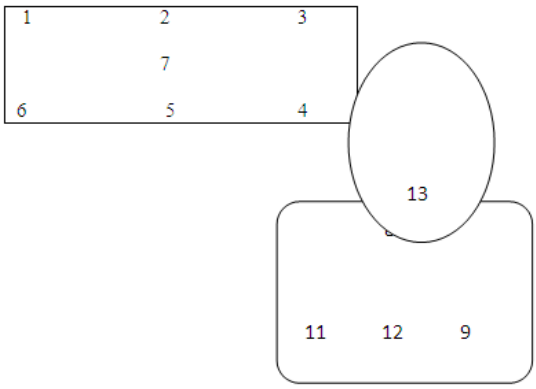

Figure: 1

Continue the blending for another 2 minutes and collect the sample from 13 locations as shown the figure.Collect samples as per the below diagram using sampling rod. The sample quantity should be between 15.3mg to 460.2mg.Bag blend Calcium stearate along with equal quantity of blend from square cone Blender in double polythene bags for 2 min. and load into square cone Blender and blend for 3 minutes and collect the sample from 13 locations as shown in the figure. The sample size after 3 minutes lubrication shall be between 155mg to 465mg.All samples shall be collected in butter paper. Collect samples in two sets. One set of sample is taken for analysis and other set is kept as a reserve sample. In case of failure results of one set use the reserve sample set for analysis, otherwise, discard the reserved sample set.

Send the sample for analysis with proper label to QC along with Analytical request form.

2.9.2Labels shall contain following details[24]

1) Date of sampling
2) Stages
3) Location No.
4) Sample no.
5) Sampled by

2.10 Compression[25,26]

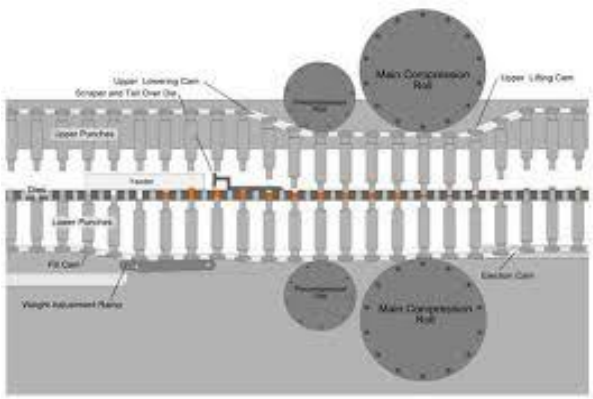

Figure 2: Compression Machine.

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product. The compression is done either by single punch machine (stamping press) or by multi station machine (rotary press). The tablet press is a high-speed mechanical device. It 'squeezes' the ingredients into the required tablet shape with extreme precision. It can make the tablet in many shapes, although they are usually round or oval. Also, it can press the name of the manufacturer or the product into the top of the tablet.[27]

Each tablet is made by pressing the granules inside a die, made up of hardened steel. The die is a disc shape with a hole cut through its center. The powder is compressed in the center of the die by two hardened steel punches that fit into the top and bottom of the die. The punches and dies are fixed to a turret that spins round. As it spins, the punches are driven together by two fixed cams - an upper cam and lower cam. The top of the upper punch (the punch head) sits on the upper cam edge .The bottom of the lower punch sits on the lower cam edge.

The shapes of the two cams determine the sequence of movements of the two punches. This sequence is repeated over and over because the turret is spinning round. The force exerted on the ingredients in the dies is very carefully controlled. This ensures that each tablet is perfectly formed. Because of the high speeds, they need very sophisticated lubrication systems. The lubricating oil is recycled and filtered to ensure a continuous supply. Common stages occurring during compression.[28]

Stage 1: Top punch is withdrawn from the die by the upper cam Bottom punch is low in the die so powder falls in through the hole and fills the die

Stage 2: Bottom punch moves up to adjust the powder weight-it raises and expels some powder

Stage 3: Top punch is driven into the die by upper cam Bottom punch is raised by lower cam Both punch heads pass between heavy rollers to compress the powder

Stage 4: Top punch is withdrawn by the upper cam Lower punch is pushed up and expels the tablet is removed from the die surface by surface plate

Stage 5: Return to stage 1.

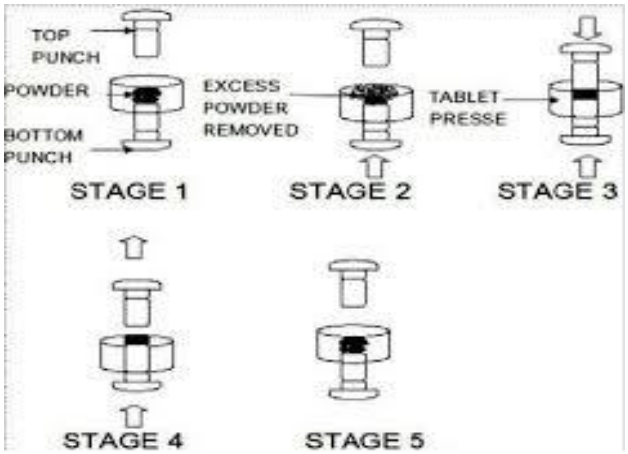

Figure 3: Stage involved in compression.

Equipment: Compression Machine
Compression to be carried out as per batch manufacturing record using 7.40 mm biconvex ,plain lower and upper punches and 7.40 mm dies. Set the machine at three different speeds of 15,25 & 35 RPM.

No. of stations: 45

Type of tooling 'D2' type

Ensure that the environmental condition (Temp & RH) in compression area are within the Prescribed Limit(Temp. 15-25˚C & RH NMT 60%).

Compression machine with attached de duster & metal detector shall be operated. All tablets shall be passed through de duster & metal detector and collected in double poly bag lined with HDPE containers.

Carry out the testing of physical parameters as mentioned in the below table.

Table 8: Shows Lists of Parameter to checked.

Parameter	Standard	Number of Tablets to be taken from each side for testing
Description	White to off white colored round uncoated biconvex tablet plain surface on both sides.	100 Tablets
Group Weight variation	2.800g ± 3.0%	20 Tablets
Individual Weight variation	Avg wt. 140 mg ±5.0%	50 Tablets
Hardness	NLT 25 N	10 Tablets
Thickness	3.30 mm ±0.20 mm	10 Tablets
Disintegration time	NMT 10 min	6 Tablets
Friability	NMT 1.0 % w/w	20 Tablets
Diameter	7.40 mm ± 0.2 mm	50 Tablets

2.10.1 Yeild of Compressed Tablet
Limit: 98.0% - 100.0 %w/w
Sampling Procedure[29]
Compression to be carried not as per batch manufacturing record using 8.0mm normal concave plain lower and upper punches and 8.0mmdies.Set the machine at three different speeds of 15,25 & 35 RPM.
No. of stations: 45
Type of tooling 'D2' type

Table 9: Shows Lists of Parameter to checked.

Parameter	Standard	Number of Tablets to be taken from each side for testing
Description	White to off white colored round uncoated biconvex tablet plain surface on both sides.	100 Tablets
Group Weight variation	2.800g ± 3.0%	20 Tablets
Individual Weight variation	Avg wt. 140 mg ±5.0%	50 Tablets
Hardness	NLT 25 N	6 Tablets
Thickness	3.30 mm ±0.20 mm	50 Tablets
Disintegration time	NMT 10 min	6 Tablets
Friability	NMT 1.0 % w/w	20 Tablets
Diameter	7.40 mm ± 0.2 mm	50 Tablets

2.11Hopper study

To evaluate effect of vibrations during compression on blend uniformity, hopper study shall be carried out. Fill the hopper completely and run the compression machine. Collect tablets when powder level in the hopper is full approximately middle of the hopper and when it is near the end of the hopper. Check the Physical parameters and testing of Content Uniformity at full, middle and near end of the hopper at optimum machine speed.

2.12 Coating[30]

Since spraying, coating distribution, and drying take place at the same time, tablet coating is a dynamic, complex process that is affected by many variables. In no particular order, here are some of the parameters that you should check when evaluating your coating operation to determine the source of defective coated tablets.

A modern tablet coating system combines several components: a coating pan, a spraying system, an airhandling unit, a dust collector, and the controls. The coating pan is actually a perforated drum that rotates within a cabinet. The cabinet enables you to control airflow, air temperature, air pressure, and the coating application. The spraying system consists of several spray guns mounted on a manifold, a solution pump, a supply tank and mixer, and an air supply. The pump delivers the coating solution to the guns, where it combines with atomizing air to create a fine mist that is directed at the bed of tablets in the coating pan. The air handling unit heats and filters the air used to dry the coating on the tablets. Depending on your circumstances, it may include a humidifier or dehumidifier. The dust collector extracts air from the coating pan and keeps a slightly negative pressure within the cabinet. The controls enable you to orchestrate the operation of all the components to achieve the desired results.

2.12.1 Tablet coating checklist2.9.1

2.12.1.1 Tablet quality. As discussed earlier, the tablets must have the proper porosity, surface, hardness, and moisture content. You can't have consistent coating without consistent tablet quality.

2.12.1.2 Waiting period. Most tablets cannot be coated immediately after they've been compressed. The energy within the tablets is still fairly high. In fact, they are still warm. In addition, tablet hardness changes over 24 to 48 hours. Let the tablets rest at least that long before you coat them.

2.12.1.3 Batch size. Variation in batch size changes the required pan speed, gun geometry, spray rates, and temperature. The more your batch sizes vary, the more quality issues that will arise in the coating process.

2.12.1.4 Solution preparation. Again, consistency is the name of the game. Does your company prepare coating solutions the same way, regardless of the batch, the shift, or the operator? Track the solution temperature, mixer speed, and storage time. All are important. Oh, and is the mixing blade correctly installed? Be sure by marking it "top" and "bottom." Spray gun calibration. You should calibrate or check the calibration of the guns every time you change products. This means checking the gun's overall condition and its filter, nozzle alignment, and needle condition.

2.12.1.5 Gun geometry. Geometry refers to the gun-to-gun alignment, gun-to-tablet bed alignment, and distance from the gun to the end of the pan. Use a ruler to be sure the distances are consistent. Furthermore, make sure all the guns are pointed in exactly the same direction and are maintaining the same spray pattern. Make certain that the tubing and connections are tight and do not interfere with alignment, which is a common problem.

2.12.1.6 Gun nozzles. The spray gun nozzles must be kept clean and free of product buildup. Use a flashlight during coating to look into the cabinet and check the nozzles.

Pan loading. While loading the tablets, look for tablets that are broken, capped, chipped, or covered with black specks. Doing so will help you pinpoint the source of any defects that occur. Do the defects appear during loading, during initial pan rotation, or after preheating? A visual inspection is critical when coating tablets that are friable or that chip or break easily.

2.12.1.7 Cleaning. Make sure you've cleaned and dried each component of the spraying system before re-installing it after a product changeover.

In tablet coating, small changes in almost any parameter can lead to big differences in results. The more consistent you make operations, and the tablet, the less you must rely on the skill of the operator. Coating may be something of an art, but you'll get better results when you apply a little science to it.

Coating to be carried out as per Batch Manufacturing Record. Before starting sub coating and enteric coating record the average weight of core tablets and sub coated tablets respectively.

Check the appearance and weight gain during coating. After completion of coating check for Description, weight variation and moisture content. Make one pooled sample for checking as per current finished product specification.

Equipment: Autocoater, colloid mill, Solution holding Tank.

2.12.2 Base Coating[31]

Required quantity of Iso propyl alcohol and dichloromethane taken in stainless steel container and colouropadry white Qy-c-7000A shall be added with

continuous stirring till to make uniform suspension and milling through colloid mill.

Above suspension shall be filtered through 100# sieve/ Muslin cloth.

Carry out the testing of pre-warm parameter as mentioned in the below table.

Table 10: Shows Lists of Parameter to check.

Parameter	Standard Limit
Duration	10-15 min.
Pan RPM	1.5-2.5 RPM
Inlet Temp.	40-50˚C
Outlet Temp.	30-40˚C
Bed Temp.	35-45˚C

Carrying out the testing of set base coating parameter after loading the tablets in coating pan as mentioned in the below table

Table 26: Shows Lists of Parameter to checked.

Parameter	Standard Limit
Pan RPM	1.0-3.0 RPM
Inlet Temp.	40±10˚C
Outlet Temp.	35±5˚C
Peristaltic pump RPM	20-60 RPM
Bed Temp.	37±5˚C
Distance of spray Gun from moving bed	07”-10”

After Base coating check and verify the parameters as given below

Table 27: Shows Lists of Parameter to checked.

Parameter	Limit
Appearance	White colored, round shaped, biconvex, enteric coated tablet
Thickness	3.40mm± 0.2
Individual Weight	142.500±5%

2.12.3 Enteric Coating

Suitable quantity of purified water shall be taken in SS container and required quantity of color acryl eze Yellow 93052098 shall be added with continuous stirring till to make uniform suspension .filter the suspension through 100# sieve/ muslin cloth.Carrying out the testing of Enteric Coating parameter as mentioned in the below table.[32]

Table 28: Shows Lists of Parameter to checked.

Parameter	Standard Limit
Pan RPM	3.0-7.0 RPM
Inlet Temp.	45±10˚C
Outlet Temp.	35±5˚C
Peristaltic pump RPM	10-35 RPM
Bed Temp.	40±5˚C
Distance of spray Gun from moving bed	7”-10”

After Enteric coating Carrying out the testing of standard parameters as given below

Table 11: Shows Lists of Parameter to checked.

Parameter	Standard Limit
Description	Yellow colored, round shape, biconvex,enteric coated tablets
Group Weight of 20 tabs.	3.180g ± 2%
Individual Weight	150.000 ± 5% mg
Thickness	3.40 mm ± 0.2
Disintegration time	0.1 HCL : No Impact on Tablets within 120Min.
	Mixed Phosphate Buffer Solution (pH6.8):NMT 60Min
Diameter	7.50 mm ± 0.2

2.12.3.1 Yeild of Coated Tablets

2.12.3.2 Limit: 97.50- 100.00%

2.12.3.3 Sampling Procedure

Coating to be carried out as per Batch Manufacturing Record. Before starting sub coating and enteric coating record the average weight of core tablets and sub coated tablets respectively .Check the appearance and weight gain during coating. After completion of coating check for Description, weight variation and moisture content. Make one pooled sample for checking as per current finished product specification.

2.13Dissolution profile

Check the dissolution profile on 12 tablets at 15 min20 min, 30 min, 45 min, and 60 min from the pooled sample after the completion of enteric coating.

Table 12: Shows Lists of dissolution sampling.

Sub-coating	Inlet temp, exhaust temp, pan speed , atomization pressure, gun distance and spray rate	Weight build up and dissolution	pooled sample 50 tablets	for information
Enteric coating	Inlet temp, exhaust temp, pan speed , atomization pressure, gun distance and spray rate	As per current finished product specifications	pooled sample	As per current finished product specifications
		Dissolution profile at 15,20,30,45a nd 60min (collect form pool sample at the end)	pooled sample	for information

2.14 Acceptance criteria for critical in process controls and sampling plan

Table 13: Shows Acceptance Criteria at each Stage.

Stage	Process variables	Sampling frequencies	Testes to be performed	Approximate sample size	Acceptance criteria
Blending	Blending time	18 and 20 min	uniformity of content and RSD	3X13 samples at each time interval between 153.4 mg to 460.2mg in butter paper	100±15% RSD NMT
		23min	uniformity of content and RSD	3X13 samples at each between 155mg to 465mg in butter paper	100±15% RSD NMT
			Bulk density ,sieve analysis, compressibility index, angle of repose, water content, and assay	100g from the blender in poly bags	for information
Compression	precompression studies at optimum speed	At lower and higher thickness	Dissolution	3X6 tablets	As per current finished product specifications
	At three different machine speeds	At different speeds	Description	50 Tablets	White to off white coloured round uncoated biconvex tablet plain surface on both sides.
			Group Weight variation	20 Tablets	2.800g ± 3.0%
			Individual Weight variation	50 Tablets	Avg wt. 140 mg ±5.0%
			Hardness	10 Tablets	NLT 25 N
			Thickness	10 Tablets	3.30 mm ±0.20 mm
			Disintegration time	6 Tablets	NMT 10 min
			Friability	20 Tablets	NMT 1.0 % w/w
			Dissolution	3×6Tablets	

3. RESULTS AND DISCUSSION

3.1Blending

Fixed Parameters
Blender RPM: 10 RPM
Blender load: 318.00 kg
Variables Considerable For Study: Blending Time
Time Intervals Studied: 18, 20 & 23 Min
Acceptance Criteria: 100±15% (RsdNmt 6.0%)
Measured Response: Content Uniformity And RSD

Batches Taken For Study: B3ACR001, B3ACR002, B3ACR003

Table 14: Shows %content uniformity at each time interval.

Batch no.	% of Pantoprazole								
	B3ACR001			B3ACR002			B3ACR003		
Blending time	18 min	20 min	23 min	18 min	20 min	23 min	18 min	20 min	23 min
1.	95.9	99	98.8	97.2	99.9	99.7	96.3	96.7	96
2.	95.2	95.6	97.8	97	96.1	97	95.9	97.2	95.9
3.	95.5	96.6	98.9	96.9	100.5	96.6	96.7	96.5	96.7
4.	97.3	97.9	98.8	97.9	99.5	97.9	98	95.8	97.1
5.	96.4	97.8	98.8	96.3	101.8	97.1	96.5	97	96.2
6.	95.7	98.5	97.3	92.8	98.6	96	96.7	98.6	99.2
7.	97.9	96.4	97.7	97	97.6	97.6	97.3	97.6	96.5
8.	95.2	96	98.1	95.8	96.4	96.7	98.1	97.9	95
9.	97.7	96.2	97.5	97.2	97.36	97.8	96.7	97.6	96.6
10.	96.6	94.5	98.7	97.4	100.5	96.5	97.2	97.1	96.1
11.	99.3	96.7	100.2	97.3	95.9	96.9	97.8	97.2	95.2
12.	95.3	100.6	97.2	97.3	101.5	98.7	98.6	96.8	94.9
13.	96.4	96.7	96.2	96.	97.3	96.7	96	95.8	98.7
Min.	**95.2**	**94.5**	**96.2**	**92.8**	**95.9**	**96**	**95.9**	**95.8**	**94.9**
Max.	**99.3**	**100.6**	**100.2**	**97.9**	**101.8**	**99.7**	**98.6**	**98.6**	**99.2**
Avg.	**96.42**	**97.11**	**98.28**	**96.62**	**98.76**	**97.32**	**97.06**	**97.06**	**96.47**
RSD	**1.32**	**1.64**	**1.01**	**1.34**	**2.07**	**1.04**	**0.87**	**0.80**	**1.34**

3.11Observations

The distribution of Pantoprazole is well acceptable as per the predetermined specification at all the intervals of blending as shown by the samples analyzed, after 23 minutes results show more closer homogeneity of pantoprazole distribution with other excipent of blend.

3.2Moisture content: As the outlet temperature reaches 60˚C, LOD is checked at every five minute until the LOD is attained within Limit (2.5-3.0%).

Table 15: Shows Moisture Content at each time interval.

	LOD of Batch No.- B3ACR001				
TIME(min.)	Inlet Air Temp	Product Temp.	Exhaust air Temp	SFM Sensitivity	LOD(%)
5	73	32	30	17	3.68
10	72	33	31	17	3.64
20	74	34	32	18	3.60
25	70	36	33	18	3.54
30	74	38	34	18	3.45
35	74	43	42	19	3.31
40	73	49	49	19	3.20
45	73	55	54	20	3.09
50	74	58	56	20	2.81

Table 16: Shows Moisture Content at each time interval.

	LOD of Batch No.- B3ACR002				
TIME(min.)	Inlet Air Temp	Product Temp.	Exhaust air Temp	SFM Sensitivity	LOD(%)
5	74	30	28	17	3.58
10	74	31	29	17	3.51
20	73	34	31	17	3.49
25	70	36	33	18	3.40
30	71	37	35	18	3.32
35	72	40	39	19	3.23
40	74	42	41	19	3.15
45	73	47	44	19	3.03
50	74	57	55	20	2.74

Table 17: Shows Moisture Content at each time interval.

	LOD of Batch No.- B3ACR003				
TIME(min.)	**Inlet Air Temp**	**Product Temp.**	**Exhaust air Temp**	**SFM Senstivity**	**LOD(%)**
5	72	30	28	16	3.69
10	72	32	29	17	3.57
20	73	31	30	17	3.52
25	70	33	31	18	3.42
30	74	35	33	18	3.34
35	72	38	35	18	3.26
40	74	41	38	19	3.17
45	73	50	46	19	3.09
50	74	59	56	20	2.87

3.3The Physical parameter of blend for Three Batches are as follows
Table 18: Shows Physical parameter.

Parameter	**B3ACR001**	**B3ACR002**	**B3ACR003**
Particle size distribution% retain on 20#	0.10%	0.06%	0.01%
% retain on 40#	24.83%	20.90%	23.17%
% retain on 60#	50.40%	36.36%	42.63%
% retain on 80#	64.53%	47.80%	55.17%
% retain on 100#	69.71%	53.12%	60.08%
% passing through 100#	29.43%	46.74%	39.22%
Untapped density g/ml	0.625	0.625	0.610
Tapped density g/ml	0.676	0.833	0.893
Compressibility index	7.50%	25.00%	31.70%
Angle of Repose	Fair	Green Zone	Yellow Zone
LOD	2.81	2.74	2.87

3.3.1Observations
The distribution of Pantoprazole is well acceptable as per the predetermined specification at all the intervals of blending as shown by the samples analyzed, after 23 minutes results show more closer homogeneity of pantoprazole distribution with other excipent of blend.

The blending time of 23 minutes is concluded validated blending time at blender 10 RPM for Pantoprazole 40 blending, when the process is performed in 1200 liters capacity Square cone blemder for a batch size of 318.00 kg. Bulk density and Particle size distribution of the lubricated blend was uniform among three batches indicates that the granulation, milling and blending process has proved to be consistent among the batches.

Particle size distribution untapped, Tapped density & angle of repose of batches are similar, Moisture content values of all three batches are also within the acceptance criteria.

3.4 Compression
VARIABLES CONSIDERED FOR STUDY: Compression speed (CADMACH).

COMPRESSION MACHINE: 45 stations
SPEEDS STUDIED: 1350, 2250 & 2700 Tablets/Minutes (15, 25&30 RPM)
MEASURED RESPONSE: Description, Group Weight variation, Individual Weight variation, Hardness, Thickness, Disintegration time &Friability

Table 19: Shows Physical parameter and standard limit.

Parameter	**Standard Limit**
Description	White to off white coloured round uncoated biconvex tablet plain surface on both sides.
Group Weight variation	2.800g ± 3.0%
Individual Weight variation	Avg wt. 140 mg ±5.0%
Hardness	NLT 25 N
Thickness	3.30 mm ±0.20 mm
Disintegration time	NMT 10 min
Friability	NMT 1.0 % w/w
Dissolution	NLT 70% in 45 min
Content uniformity **RSD**	100 ± 15% NMT 6.0%

Acceptance Criteria: NLT 75 %
Table 20: Shows Dissolution at each thickness.

	% of Pantoprazole								
Batch No.	**B3ACR001**			**B3ACR002**			**B3ACR003**		
M/C Speed (RPM)	**Lower**	**Optimum**	**Higher**	**Lower**	**optimum**	**higher**	**Lower**	**Optimum**	**higher**
1	92.6	100.4	95.5	99.8	99.1	104.8	100.1	101.2	101.6
2	99.1	100	100.8	95.8	101.4	101.9	99.5	100	101.8
3	86.9	101.6	99.6	98.6	97	99.9	99.2	99.6	101.9
4	101.3	99.2	100.3	96.3	101.2	99.9	99.2	103.8	102
5	103.2	99.3	99.7	97.6	96.1	101.9	99.1	97.7	99.2
6	96.1	101.8	101.1	99.3	98.5	104.4	95.9	99.1	100.3
Min.	**86.9**	**99.2**	**95.5**	**95.8**	**96.1**	**99.9**	**95.9**	**97.7**	**99.2**
Max.	**103.2**	**101.8**	**101.1**	**99.8**	**101.4**	**104.9**	**100.1**	**103.8**	**102**
Avg.	**96.53**	**100.38**	**99.5**	**97.9**	**98.88**	**102.63**	**98.83**	**100.23**	**101.13**

Observations: Pre compression dissolution at lower, optimum and higher thickness complies with acceptance criteria.

Table Dissolution of pantoprazole tablets compressed at different speeds 15, 25, 30 RPM for the batch no. B3ACR001, B3ACR002, B3ACR003

Table 21: Shows Dissolution at different Speed.

	% of Pantoprazole								
Batch No.	**B3ACR001**			**B3ACR002**			**B3ACR003**		
M/C Speed (RPM)	**15**	**25**	**30**	**15**	**25**	**30**	**15**	**25**	**30**
1	95.9	97.2	101	100.9	98.5	102.9	98.3	99.8	99
2	94.5	97.2	100.2	98.6	98.4	100.6	98.8	99.2	98.5
3	97.2	96.9	98.9	102.3	100.2	99.3	98.7	101.1	102
4	94.5	96.9	99.1	99.8	99.9	99.9	97.8	99.3	98.6
5	100.5	97.1	96.3	99.8	100.3	101.2	100.2	99.3	99.8
6	101	96.6	99.7	100.4	98.9	98	98.7	98.1	100.6
Min.	**94.5**	**96.6**	**96.3**	**98.6**	**98.4**	**98**	**97.8**	**98.1**	**98.5**
Max.	**101**	**97.2**	**101**	**102.3**	**100.3**	**1022.9**	**100.2**	**101.1**	**102**
Avg.	**97.16**	**96.98**	**99.2**	**100.3**	**99.37**	**100.32**	**98.75**	**99.47**	**99.75**

Table Content uniformity of pantoprazole 40 tablets compressed at different speeds 15, 25, 30 RPM for the batch no. B3ACR001, B3ACR002, B3ACR003

Acceptance Criteria: 100 ± 15 % (Max.-115, Min-85)

Table 22: Shows % Content Uniformity at different Speed.

	% of Pantoprazole								
Batch No.	**B3ACR001**			**B3ACR002**			**B3ACR003**		
M/C Speed (RPM)	**15**	**25**	**30**	**15**	**25**	**30**	**15**	**25**	**30**
1	98.9	101.1	99.5	95.1	97.1	97	99.2	100	101.2
2	99.2	99.6	101.2	99.1	97.9	99.1	99.1	99.6	100.6
3	99.5	100.6	100.7	97.8	102.8	101.7	101	101.4	99.6
4	100	99	99.4	100.5	102.2	100.7	99.1	99	99.7
5	99.4	99.8	100	100	100.3	97.2	100.9	101.2	99.3
6	102	100.4	100.1	97.5	101.5	97.9	99.9	100.2	100.6
7	99.2	98.7	99.1	982	97.5	101.4	103.1	100.9	101.7
8	100.1	99.8	99.3	96.6	101.5	99.5	101.2	101.9	102.2
9	100.3	100.6	100.7	99.1	98.7	98.4	99.4	99.4	99.6
10	99.6	100.2	99.5	102	99.4	98.4	100.5	99.6	100.8
Min.	**98.9**	**98.7**	**99.1**	**95.1**	**97.1**	**97**	**99.1**	**99**	**99.3**
Max.	**102**	**101.1**	**101.2**	**102**	**102.8**	**101.7**	**103.1**	**101.9**	**102.2**
Avg.	**99.82**	**99.99**	**99.95**	**98.59**	**99.89**	**99.13**	**99.87**	**100.23**	**100.17**

3.5Coating
CoatingMACHINE: Autocoater 60”

Pan RPM STUDIED: 1-7 rpm
Perstaltic RPM Studied: 20-60 rpm.

3.5.1For base coating

Table 23: Shows Parameter & Standard Limit.

Parameter	Standard Limit
Pan RPM	1.0-3.0 RPM
Inlet Temp.	40±10˚C
Outlet Temp.	35±5˚C
Peristaltic pump RPM	20-60 RPM
Bed Temp.	37±5˚C
Distance of spray Gun from moving bed	07”-10”
Appearance	White coloured, round shaped, biconvex, enteric coated tablet
Thickness	3.40mm± 0.2
Individual Weight	142.500±5%

3.5.2 For Enteric Coating

Table 24: Shows Parameter&Standard Limit.

Parameter	Standard Limit
Pan RPM	3.0-7.0 RPM
Inlet Temp.	45±10˚C
Outlet Temp.	35±5˚C
Peristaltic pump RPM	10-35 RPM
Bed Temp.	40±5˚C
Distance of spray Gun from moving bed	7”-10”
Description	Yellow colored, round shape, biconvex,enteric coated tablets
Group Weight of 20 tabs.	3.180g ± 2%
Individual Weight	150.000 ± 5% mg
Thickness	3.40 mm ± 0.2
Disintegration time	0.1 HCL : No Impact on Tablets within 120Min.
	Mixed Phosphate Buffer Solution (pH6.8):NMT 60Min
Diameter	7.50 mm ± 0.2

3.5.3Coating Identification

3.5.3.1 Measurement Properties

WavelengthRange : 230.00 to 350.00 nm
Scan Speed : Medium
Sampling Interval : 0.1
Scan Mode : Single

3.5.3.2 Instrument Properties

Instrument Typr : UV-1800 Series
Measuring Mode : Absorbance
Slit Width : 1.0 nm

Table 25

3.5.3.3 Coating identification of Batch No. B3ACR001.

S. No.	Wavelength	Absorbance
1	349.10	0.008
2	346.40	0.007
3	289.70	0.523

Table 26

3.5.3.4 Coating identification of Batch No. B3ACR002.

S.No.	Wavelength	Absorbance
1	348.20	0.022
2	344.60	0.022
3	289.70	0.501

3.5.3.5 Coating identification of Batch No. B3ACR003.

S. No.	Wavelength	Absorbance
1	348.00	0.008
2	343.50	0.009
3	289.00	0.494

3.6 Calculation sheet For Dissolution Test

3.6.1Calculation sheet For Dissolution Test for Batch No. B3ACR001

Standard Absorbance : 0.740
% Potency : 93.91%

Table 27: Show Dissolution Test Result.

S. No.	Sample	Wavelength (290.0)
1	Blank	0.000
2	Standard	0.740
3	DR_1	0.736
4	DR_2	0.767
5	DR_3	0.743
6	DR_4	0.755
7	DR_5	0.733
8	DR_6	0.702

Table 28: Show Test Result and % content of Test sample.

	Area/Absorbance	% content
Tablet-1	0.736	103.52
Tablet-2	0.767	107.88
Tablet-3	0.743	104.51
Tablet-4	0.755	106.19
Tablet-5	0.733	103.10
Tablet-6	0.702	98.74

%Minimum - 98.74
% Maximum - 107.88
% Average - 103.99
% RSD - 3.006

3.6.2 Calculation sheet For Dissolution Test for Batch No. B3ACR002
Standard Absorbance : 0.732
% Potency : 93.91%

Table 29: Show Dissolution Test Results.

	Area/Absorbance	% content
Tablet-1	0.739	105.08
Tablet-2	0.710	100.96
Tablet-3	0.747	106.22
Tablet-4	0.715	101.67
Tablet-5	0.745	105.93
Tablet-6	0.725	103.09

% Minimum -100.96
% Maximum – 106.22
% Average - 103.82
% RSD - 2.161

3.6.3 Calculation sheet For Dissolution Test for Batch No. B3ACR003
Standard Absorbance : 0.731
% Potency : 93.91%

Table 30: Show Test Result and % content of Test sample.

	Area/Absorbance	% content
Tablet-1	0.737	104.94
Tablet-2	0.739	105.22
Tablet-3	0.699	99.53
Tablet-4	0.708	100.81
Tablet-5	0.757	107.79
Tablet-6	0.730	103.94

% Minimum -99.53
% Maximum – 107.79
% Average - 103.71
% RSD - 2.937

Table: Content uniformity of pantoprazole 40 coatedtablets for the batch no. B3ACR001, B3ACR002, B3ACR003.

Acceptance Criteria: 100 ± 15 % (Max.-115, Min-85)

3.7 Content Uniformity
Table 29: Shows % Content Uniformity.

% of Pantoprazole			
Batch No.	**B3ACR001**	**B3ACR002**	**B3ACR003**
1.	95.9	99.0	98.8
2.	95.2	95.6	97.8
3.	95.5	96.6	98.9
4.	97.3	97.9	96.2
5.	96.4	97.8	98.8
6.	95.7	98.5	97.3
7.	97.9	96.4	97.7
8.	95.2	96	100.2
9.	97.7	96.2	97.5
10.	99.3	100.6	98.7
Min.	**95.2**	**95.6**	**96.2**
Max.	**99.3**	**100.6**	**100.2**
Avg.	**96.42**	**97.11**	**98.28**

CONCLUSION

Process validation of pantoprazole 40mg tablets was conducted, which included the validation of critical steps of manufacturing such as blending, compression and coating.

Blending: The blending was performed and the samples at the designated locations were drawn after 18,20 and 23 min of blending for determination of the content uniformity and RSD values of pantoprazole. The RSD the values meet the acceptance criteria at the all the 3 blending intervals. From the analytical results it is clear that the drug distribution pattern in the blend is almost homogeneous.

Compression: The compression was carried out between the speed limits and physical parameters of the tablets were studied at this speed. The parameters checked included appearance, individual weight variation, group weight variation, thickness of tablets, hardness of tablet, tablet friability and tablet disintegration time. The parameters are well within the limits of acceptance criteria at the speed s studied. Hence the compression stage of pantoprazole 40 is consistent and reproducible when the compression was carried out at the speeds of 15, 25, 30 rpm. Content uniformity and dissolution of compressed tablets of all three speeds of compression stage are found to be uniform and well within the limits of acceptance criteria. Hopper study was carried out for full hopper, half hopper and near end hopper to establish the segregation of the blend during compression.

Sub coating: The sub coating validation was carried out and found that all the physical and chemical parameters of subcaoted tablets are well within the limits of acceptance criteria when coating is performed with the recommended coating parameters dissolution data of sub coated tablets well within the limits. The weight build up is 19 mg to 23 mg.

Enteric coating: The enteric coating validation for the three batches was carried out in Autocoater of 60" for batch size of 20.0 lacs. tablets and found that all the physical chemical parameters of coated tablet are well within the limits of acceptance criteria. Dissolution profile of coated tablet are well within the limits of acceptance criteria the weight build up is 20mg to 22mg. over all 3mg per tablet of extra enteric coating material are taken to achieve above enteric weight buildup.

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