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PROCESS VALIDATION OF THE MIRABEGRON EXTENDED RELEASE TABLETS 50 MG

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ABSTRACT:

The purpose of this study was to evaluate the relationship among numerous variables to enhance the understanding of the effects of materials and process parameters on drug product quality and to develop a validated method for manufacturing of Mirabegron Extended Release Tablets 50 MG. Mirabegron is selected drug which is beta-3 adrenergic agonists used for relaxing the bladder muscles to prevent urgent, frequent, or uncontrolled urination. Effect of various process parameters such as, Dry mixing time and impeller speed, binder addition, and kneading time, impeller speed, chopper speed, drying inlet temperature, outlet temperature, LOD, Multi-mill speed, mixing time / blending time were studied on product quality.

1. Introduction:

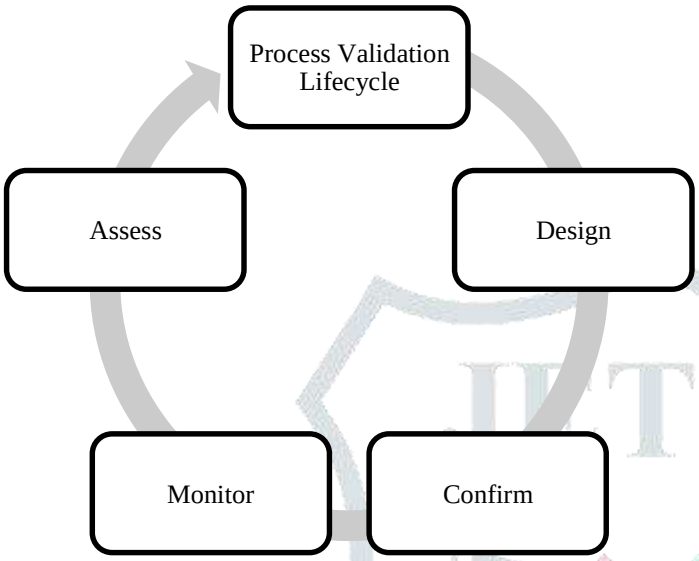
Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics.

1.1 Steps in Validating a Process:

- Development Sequence
- Development stage Pilot scale-up phase
- Product design
- Product characterization
- Product selection
- Process design

- Product optimization
- Process characterization
- Process optimization
- Process demonstration
- Process validation program
- Product/process certification

1.2 Life Cycle of Validation:



1.3 Importance of Process validation -

Process validation provides high degree of assurance of quality of product by reducing the quality differences in batches by providing significant process parameters and controls. It helps to find out faults in manufacturing process and to avoid these faults in future. It minimal the chances of batch failures and reduces the wastage of material and increase the productivity.

1.4 Stages of process validation -

- **Process Design** – The commercial manufacturing process is **defined**.
- **Process Qualification** – The design is **evaluated** to determine whether the processes meet demands of reproducibility.
- **Continued Process Verification** – Ongoing assurances that all processes remain in a **state of control.**

1.5 GMP requirements for Process Design

- Design of Facility
- Design of Equipment
- Design of Production and Control Procedures
- Design of Laboratory Controls
- Propose process steps (unit operations) and process variables (operating parameters) that need to be studied.
- Identify sources of variability each unit operation is likely to encounter.
- Consider possible range of variability for each input into the operation.
- Evaluate process steps and variables for potential criticality.
- Select process steps and variables for test in representative models.

- Development studies to identify critical operation parameters and operating ranges
- Designed experiments
- Lab scale, pilot scale and/or full scale experimental batches to gain process understanding
- Establish mechanisms to limit or control variability based on experimental data
- Aim for a "robust process", i.e., one that can tolerate input variability and still produce consistent acceptable output

1.6 Types of Validation

- Prospective validation
- Concurrent Validation
- Retrospective Validation
- Revalidation

Prospective validation: The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. Prospective validation should normally be completed prior to the distribution and sale of the medicinal product. In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol [Sumeet et al, 2013].

Concurrent validation: It is a process where current production batches are used to monitor processing parameters. It gives of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch. Concurrent Validation means establishing documented evidence a process does what it is supposed to base on data generated during actual implementation of the process. Concurrent validation may be the practical approach under certain circumstances. It is important in these cases when the systems and equipment to be used have been fully validated previously [Sumeet et al, 2013].

Retrospective validation: Conducted fir a product already being marked, and is based on extensive data accumulated over several lots and over time. Retrospective Validation may be used for older products which were not validated by the fabricator at the time that they were first marketed, and which is now to be validated to confirm to the requirements of division 2, Part C of the Regulation to be Food and Drugs Act. Retrospective Validation is only acceptable for well-established detailed processes and will be Inappropriate where there have recent changes in the formulation of the products, operating procedures, equipment and facility [Sumeet et al, 2013].

Revalidation: Re-validation is usually performed to the confirmation of initial validation for a Periodic review. Re-validation provides the evidence that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process. Re-validation becomes necessary in certain situations [Sumeet et al, 2013].

Keywords: Process Validation ,Mirabegron ,Lifecycle of Drug.

2. Material and Method:

Material used: Mirabegron Tablet 50 mg.

2.1 Product Details:

Product Name: Mirabegron Tablet 50 mg.
Generic Name : Mirabegron Extended Release tablet

2.2 Equipment Detail:

S.No.	Equipment Details
1.	Vibro Sifter
2.	Wurster Coater Combo
3.	Multi Mill
4.	Mechanical Stirrer
5.	Solution preparation vessel
6.	Octagonal Blender (150 L)
7.	Compression Machine
8.	Deduster Machine
9.	Metal detector
10.	Auto coater (26")
11.	Mechanical Stirrer
12.	Solution preparation vessel
13.	Alu-Alu Blister Packing Machine

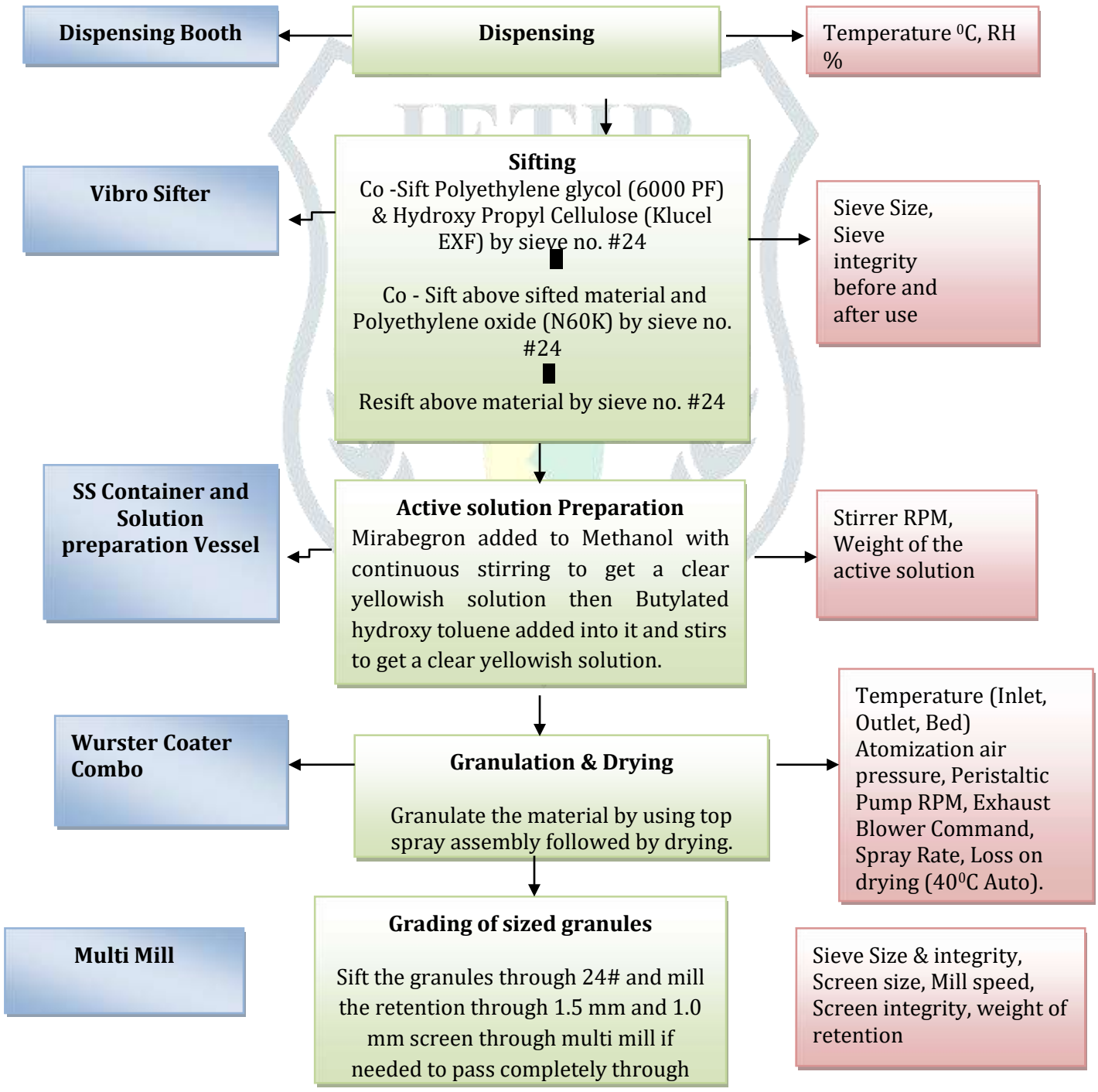
2.3 Method:

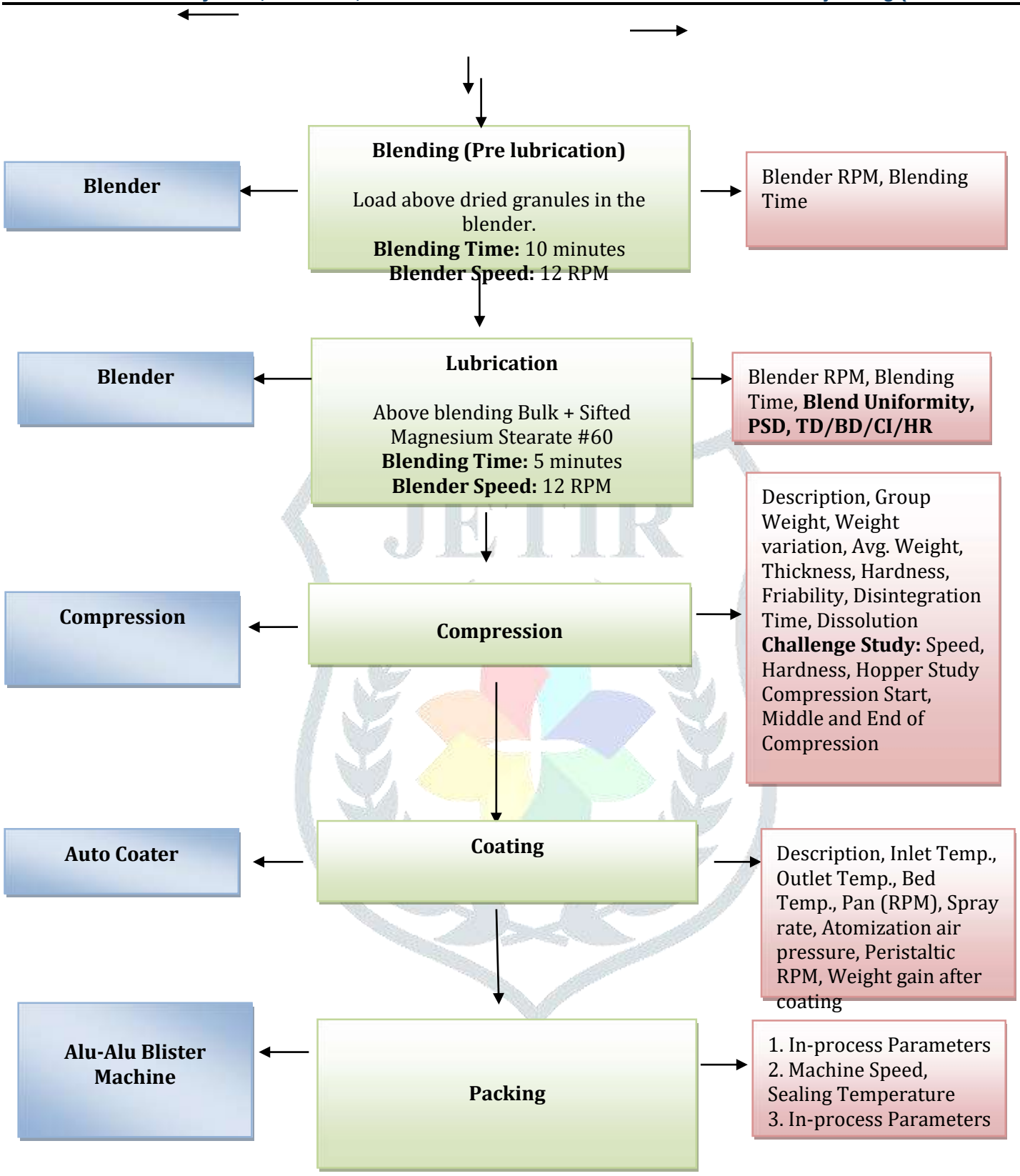
Three consecutive batches for process validation of the product Mirabegron Tablets 50 mg shall be manufactured as per approved master batch manufacturing record and shall be tested as per approved standard testing procedure to demonstrate compliance with the approved specifications.

Three validation batches were manufactured and packed and details as:

Sr. No.	Generic Name	Batch No.	Batch Size
1.	Mirabegron Extended-Release Tablets 50 mg.	A21	1,50,000 tablets
2.	Mirabegron Extended-Release Tablets 50 mg.	B21	1,50,000 tablets
Sr. No.	**Generic Name**	**Batch No.**	**Batch Size**
3.	Mirabegron Extended-Release Tablets 50 mg.	C21	1,50,000 tablets

2.4 Manufacturing Details:




Blending (Pre lubrication)
Load above dried granules in the blender.
Blending Time: 10 minutes
Blender Speed: 12 RPM
Blender
Blender RPM, Blending Time
Lubrication
Above blending Bulk + Sifted Magnesium Stearate #60
Blending Time: 5 minutes
Blender Speed: 12 RPM
Blender
Blender RPM, Blending Time, Blend Uniformity, PSD, TD/BD/CI/HR
Compression
Description, Group Weight, Weight variation, Avg. Weight, Thickness, Hardness, Friability, Disintegration Time, Dissolution
Challenge Study: Speed, Hardness, Hopper Study Compression Start, Middle and End of Compression
Compression
Coating
Auto Coater
Description, Inlet Temp., Outlet Temp., Bed Temp., Pan (RPM), Spray rate, Atomization air pressure, Peristaltic RPM, Weight gain after coating
Packing
Alu-Alu Blister Machine
1. In-process Parameters
2. Machine Speed, Sealing Temperature
3. In-process Parameters

2.5 Process Risk on the product Critical Quality Attributes:

Drug Product CQA	Process Steps						
	Sifting	Granulation	Drying	Sifting & Milling	Blending/ Lubrication	Compression	Film Coating
Assay	Low	Low	Low	Low	Low	Medium	Low
Blend / Content Uniformity	Low	Low	Low	Low	Medium	Medium	Low
Dissolution	Low	Medium	Low	Low	Low	Medium	Low
Related Substances	Low	Low	Medium	Low	Low	Low	Low

2.6 Manufacturing process evaluation

S. No.	Process Parameter	Equipment ID	Critical variable	Acceptance Criteria	Observation		
					A21	B21	C21
1.	Dispensing (API)	Dispensing Booth	Temperature (ºC)	NMT 25ºC	20.4 ºC	20.9 ºC	19.4 ºC
			Relative Humidity (%)	NMT 50%	042 %	035 %	048 %
	Dispensing (Excipients)		Temperature (ºC)	NMT 25ºC	19.1 ºC	23.2 ºC	21.4 ºC
			Relative Humidity (%)	NMT 50%	038 %	039 %	038 %
	Dispensing (Coating)		Temperature (ºC)	NMT 25ºC	19.1 ºC & 20.5 ºC	20.4 ºC	21.4 ºC
			Relative Humidity (%)	NMT 50%	038 %	035 %	038 %
	Dispensing (Solvent)		Temperature (ºC)	NMT 25ºC	20.8 ºC	21.1 ºC	21.9 ºC
			Relative Humidity (%)	NMT 60%	043 %	030 %	033 %
2.	Co-Sifting	Vibro sifter MF/VBS/09)	Sieve Size	#24	#24	#24	#24
			Sieve integrity Before	Should be intact	Found intact	Found intact	Found intact
			After	Should be intact	Found intact	Found intact	Found intact

	Re-sift the material through # 24 sieve	Vibro sifter (MF/VBS/09 & MF/VBS/07)	Total wt. of mixed material	To be recorded	29.520 kg	29.515 kg	29.390 kg
3.	**Drug Solution Preparation** Weight the separate of 127.500 kg. (For Solution preparation) and 3.750 kg. (for vessel rinse) of Methanol into cleaned suitable SS container.	Solution Preparation Vessel	Qty. of Methanol	127.500 kg.	127.500 kg	127.500 kg	127.500 kg
			Mirabegron IP Sol ution Description	Should be Clear Yellowish Solution	Clear Yellowish Solution	Clear Yellowish Solution	Clear Yellowish Solution
			Stirring Time	To be recorded	18 min.	69 min.	46 min.
			Butylated Hydrox y Toluene Solution Descripti on	Should be Clear Yellowish Solution	Clear Yellowish Solution	Clear Yellowish Solution	Clear Yellowish Solution
			Stirring Time	To be recorded	13 min.	28 min.	07 min.
			Net wt. of yellowi sh solution	To be recorded	134.940 kg	134.640 kg	134.140 kg
4.	Wurster Coater Combo Finger Bag		Finger Bag integrity — Before	Should be intact	Found intact	Found intact	Found intact
			After	Should be intact	Found intact	Found intact	Found intact
		Wurster Coater Combo MF/WCC/01					
5.	Wurster Coater Combo Bowl Sieve (Dutch Mesh)		Bowl integrity — Before	Should be intact	Found intact	Found intact	Found intact
			After	Should be intact	Found intact	Found intact	Found intact
6.	Granulation (Top Spraying)		No. of guns	01	01	01	01
			No. of Nozzle	01	01	01	01
			Size of Nozzle	2.0 mm	2.0 mm	2.0 mm	2.0 mm
			Inlet Air Temperature	25°C to 40°C (Tentative)	34-35°C	35-37°C	35°C

			Observation →		27-36°C	28-38°C	*23-36°C
			Bed Temperature (°C)	20°C to 35°C (Tentative)	23-31°C	21-24°C	*17-27°C
			Outlet temperature (°C)	To be recorded	21-30°C	20-25°C	16-25°C
			Peristaltic Pump RPM	To be recorded	65-75 RPM	65-75 RPM	60-70 RPM
			Spray rate (g/min)	130 to 160 g/min (Tentative)	140-160 g/min	140-160 g/min	*120-160 g/min
			Atomization Air Pressure	NLT 2.5 kg/cm^2 (Tentative)	2.5 kg/cm^2	2.5 kg/cm^2	2.5 kg/cm^2
			Exhaust Blower Command	30 - 80% (Tentative)	10-17 %	10-14 %	10-22 %
			CFM	To be recorded	406-847 CFM	390-781 CFM	434-910 CFM
			*Initial value may be lower side. However, limits are tentative and shall be finalized after PV recommendation.				
7.	Drying		Inlet Temperature (°C)	30 - 40°C (Tentative)	35 °C	37 °C	35 °C
			Observation →		33 - 36 °C	32 - 37 °C	35 °C
			Outlet Temperature (°C)	To be recorded	25 - 27°C	24 - 27°C	24 - 29°C
			Bed Temperature (°C)	25 - 40°C (Tentative)	31 – 34 °C	30 – 34 °C	26 – 32 °C
			Exhaust Blower Command	30 – 80 % (Tentative)	17 %	14 %	25 %
			CFM	To be recorded	695 – 712 CFM	614 – 674 CFM	810 – 872 CFM
			Total Drying Time (min.)	To be recorded	05 min.	05 min.	09 min.
			LOD (% w/w)	NMT 1.0% w/w at 40°C (Auto mode).	0.21 %	0.79 %	0.18 %
8.	**Sifting & Sizing**	Vibro sifter (MF/VBS/09)	Sieve Size	#24	#24	#24	#24
			Sieve integrity — Before	Should be intact	Found intact	Found intact	Found intact

	Size the dried granules using of multi-mill and collect in Double line	Multi-mill MF/MLM/03 MF/MLM/04		After	Should be intact	Found intact	Found intact	Found intact
			Amount of mass retained #24		To be recorded	8.210 kg 5.205 kg	8.115 kg 2.175 kg	15.000 kg
			Speed of multi mill		To be recorded	1500	1500	1500
			Knives direction		Forward	Forward direction	Forward direction	Forward direction
	polybag.		Screen Size (mm)		1.5 mm, 1.0 mm	1.5 mm & 1.0 mm	1.5 mm & 1.0 mm	1.5 mm & 1.0 mm
			Screen integrity	Before	Should be intact	Found intact	Found intact	Found intact
				After	Should be intact	Found intact	Found intact	Found intact
9.	Sifting of Lubricants	Vibro sifter (MF/VBS/09)	Sieve Size		#60	#60	#60	#60
			Sieve integrity	Before	Should be intact	Found intact	Found intact	Found intact
				After	Should be intact	Found intact	Found intact	Found intact
Blending								
10.	Pre-lubrication	Octagonal Blender MF/OGB/01	Blending Time (min.)		10 minutes	10 min.	10 min.	10 min.
			Blender RPM		12 RPM	12 RPM	12 RPM	12 RPM
11.	Lubrication		Blending Time (min.)		05 minutes	05 min.	05 min.	05 min.
			Blender RPM		12 RPM	12 RPM	12 RPM	12 RPM
			Net Blend (qty.)		To be recorded	35.800 kg	35.400 kg	35.785 kg
12.	Blend Yield		Reconciliation		NLT 95.0 % (Tentative)	96.94 %	98.11 %	96.91 %
			Actual Yield		NLT 95.0 % (Tentative)	97.16 %	98.59 %	96.96 %

S. No.	Process Parameter	Equipment ID	Critical variable	Acceptance Criteria	Observation		
					A21	B21	C21
1.	Compression	MF/COM/06	Punch description	11.90 mm X 5.90 mm, oval shape standard concave, embossed "50"	11.90 mm X 5.90 mm, oval shape standard concave, embossed "50"	11.90 mm X 5.90 mm, oval shape standard concave, embossed "50"	11.90 mm X 5.90 mm, oval shape standard concave, embossed "50"
			Upper Punch	Embossed "50"	Embossed "50"	Embossed "50"	Embossed "50"
			Lower Punch	Plain	Plain	Plain	Plain
			Description	Oval shaped, white to slightly yellowish white, uncoated tablets, debossed "50" on one side and plain on other side.	Oval shaped, white to slightly yellowish white, uncoated tablets, debossed "50" on one side and plain on other side.	Oval shaped, white to slightly yellowish white, uncoated tablets, debossed "50" on one side and plain on other side.	Oval shaped, white to slightly yellowish white, uncoated tablets, debossed "50" on one side and plain on other side.
			Group Weight of 20 Tablets	5.000 gm ± 3% (4.850 g – 5.150 g)	5.017- 5.046 g	5.003- 5.086 g	4.989- 5.109 g
			Average weight	250.00 mg ± 3.0 % (242.500 mg to 257.500 mg)	250.2 – 251.0 mg	249.9 – 251.028 mg	250.2 – 251.901 mg
			Uniformity of weight	250.00 mg ± 5.0 % (237.500 mg to 262.500 mg)	245 – 255 mg	246 – 256 mg	245 – 256.70 mg
			Length (mm)	11.90 mm ± 0.2 mm	11.89 – 11.93 mm	11.87 – 11.94 mm	11.90 – 11.95 mm
			Width (mm)	5.90 mm ± 0.2 mm	5.89 – 5.92 mm	5.89 – 5.94 mm	5.90 – 5.95 mm
			Hardness of 5 tablets (N)	70 N ± 40 N [30 N to 110 N]	35.1 – 65.0 N	52.8 –76.3 N	35.8 – 52.2 N
			Thickness of 5 tablets (mm)	4.4 ±0.3 mm (4.10 mm to 4.70 mm)	4.25 – 4.52 mm	4.34 – 4.50 mm	4.30 – 4.55 mm
			Friability (% w/w)	NMT 1.0% w/w	0.09 – 0.20 %	0.09 – 0.18 %	0.11 – 0.24 %
			Machine Speed (RPM)	To be recorded	15 – 50 RPM	30 RPM	15-20 RPM
			Force Feeder Speed (RPM)	To be recorded	12 – 20 RPM	15 RPM	10 RPM

			Fill depth	To be recorded	6.64 – 7.00	7.54 – 7.61	6.21 – 6.37
			1st compression force	To be recorded	1.6 – 1.7	1.8 – 1.9	1.4 – 1.9
			2nd compression force	To be recorded	2.7 – 7.4	6.6 – 6.9	3.6 – 5.3
2.	Compression Yiel d		Actual Yield	NLT 95.0 % (Tentative)	95.37 %	96.92 %	*94.17 %
			Reconciliation	NLT 95.0 % (Tentative)	99.14 %	99.52 %	99.09 %

S. No.	Process Parameter	Equipment ID	Critical variable	Acceptance Criteria (Lot -I & II)	Observation				
					B. No. MAM21001WD			B. No. B21	B. No. C21
					Lot-I	Lot-II	Lot-III@		
1.	Film Coating solution	Auto Coater MF/ACO/01	Stirring Time (min.)	45 minutes	45 min.	45 min.	45 min.	45 min.	45 min.
			Qty. of coating solution	To be recorded	3.080 kg	3.080 kg	2.060 kg	6.200 kg	6.200 kg
2.	Film Coating		Pan Size	26 inches	26 inches			37 inches	37 inches
			Number of spray guns	02	02			03	03
			Nozzle Diameter (mm)	1.5 mm	1.5 mm			1.5 mm	1.5 mm
S. No.	**Process Parameter**	**Equipment ID**	**Critical variable**	**Acceptance Criteria (Lot -I & II)**	**Observation**				
					B. No. MAM21001WD			**B. No. B21**	**B. No. C21**
					Lot-I	**Lot-II**	**Lot-III@**		
			Gun to Gun Distance (cm)	To be recorded	16.5 cm			15 cm	15 cm
			Gun to Bed Distance (cm)	12.7 – 17.78 cm (Tentative)	13 cm			16 cm	15 cm
3.	Film Coating (Pre-heating)		Pre-heating Time (min.)	10 minutes	10 min.	10 min.	10 min.	10 min.	10 min.
			Inlet Temperature (ºC)	40 - 50ºC	45.5 – 46.1 ºC	45.2- 50.0 ºC	47.1 – 50.1 ºC #	46.3 – 48.5 ºC	43.2 – 46.0 ºC
			Exhaust Temperature (ºC)	To be recorded	31.6 – 35.6 ºC	36.1 – 40.8 ºC	37.2 – 41.6 ºC	37.4 – 37.5 ºC	32.0 – 37.0 ºC
			Bed Temperature (ºC)	30 - 45ºC	*29.1 – 36.1 ºC	31.4 – 39.1 ºC	*29.1 – 42.1 ºC	34.1 – 37.4 ºC	32.1 – 41.4 ºC
			*Initial value observed at lower side hence it is not considered. #Inlet temperature observ ed out of limit. However, limit is tentative and shall be finalized after PV report recommendation.						

			Pan Speed (RPM)	To be recorded	1.0 RPM	1.0 RPM	1.0 RPM	1.0 RPM	1.0 RPM
4.	Film Coating (Coating Stage)		Inlet Temperature (ºC)	35 - 50ºC	46.2 – 58.0 ºC*	*54.1 – 58.0 ºC	*53.1 – 58.0 ºC	*45.0 – 55.0 ºC	44.9 – 48.1 ºC
			Outlet Temperature (ºC)	To be recorded	33.8 – 42.7 ºC	38.9 – 43.4 ºC	39.3 – 41.8 ºC	35.2 – 43.9 ºC	34.9 – 36.8 ºC
			Bed Temperature (ºC)	30 - 45ºC	33.5 – 46.0 ºC	39.8 – 43.9 ºC	39.4 – 42.7 ºC	34.1 – 40.4 ºC	37.8 – 40.5 ºC
			Atomization air pressure	To be recorded	2.0	2.0	2.0	2.0	2.0
			Spray rate (gm/min.)	To be recorded	36 – 44 g/min.	36 -40 g/min.	32 – 36 g/min.	44 – 56 g/min.	56 – 68 g/min.
			Pan Speed (RPM)	3 - 8 RPM	3.0 – 8.0 RPM	3.0 – 7.0 RPM	4.0 – 7.0 RPM	3.0 – 8.0 RPM	4.0 – 8.0 RPM
			Peristaltic Pump RPM	To be recorded	10 – 12 RPM	10 RPM	10 RPM	10-12 RPM	12-14 RPM
S. No.	**Process Parameter**	**Equipment ID**	**Critical variable**	**Acceptance Criteria (Lot -I & II)**	**Observation**				
					B. No. MAM21001WD			**B. No. B21**	**B. No. C21**
					Lot-I	**Lot-II**	**Lot-III@**		
			*Inlet temperature observ ed at higher side, however, limit is tentative and shall be fin alized after PV report recommendation.						
5.	Film Coating (Drying Stage)		Drying Time (min.)	15 to 25 minutes	20 min.	20 min.	20 min.	15 min.	25 min.
			Inlet Temperature (ºC)	To be recorded	50.0 – 55.4 ºC	50.0 – 56.4 ºC	49.9 - 54.4 ºC	49.7 – 51.1 ºC	44.9 – 47.7 ºC
			Outlet Temperature (ºC)	To be recorded	43.3 – 44.7 ºC	43.4 – 44.0 ºC	42.5 – 42.6 ºC	43.6 – 45.3 ºC	37.1 – 38.0 ºC
			Bed Temperature (ºC)	To be recorded	45.6 – 46.5 ºC	44.7 – 44.9 ºC	44.0 – 44.7 ºC	44.7 – 43.3 ºC	40.6 – 41.2 ºC
			Pan Speed (RPM)	To be recorded	1.0 RPM	1.0 RPM	1.0 RPM	1.0 RPM	1.0 RPM
6.	Film Coating (Cooling Stage)		Cooling Time (min.)	To be recorded	15 min.	15 min.	15 min.	20 min.	20 min.
			Pan Speed (RPM)	To be recorded	1.0 RPM	1.0 RPM	1.0 RPM	1.0 RPM	1.0 RPM
			Outlet Temperature (ºC)	To be recorded	35.1 – 43.2 ºC	34.5 – 42.5 ºC	33.2 – 41.8 ºC	33.6 – 44.4 ºC	35.5 – 29.7 ºC
			Bed Temperature (ºC)	To be recorded	34.6 – 45.5 ºC	37.6 – 45.0 ºC	33.6 – 44.2 ºC	32.9 – 43.1 ºC	28.2 – 38.0 ºC

7.	Physical Parameters (Coated Tablets)		Weight gain (% w/w)	NLT 2.0 % w/w	2.18 % w/w	2.48 % w/w	2.30 % w/w	2.07 % w/w	2.10 % w/w
			Description	Yellow coloured, oval shaped, biconvex, film coated tablets,	Yellow coloured, oval shaped,	Yellow coloured, oval shaped,	Yellow coloured, oval shaped,	Yellow coloured, oval shaped, biconvex, film coated tablets,	Yellow coloured, oval shaped, biconvex, film coated tablets,
S. No.	**Process Parameter**	**Equipment ID**	**Critical variable**	**Acceptance Criteria (Lot -I & II)**	**Observation**				
					B. No. MAM21001WD			**B. No. B21**	**B. No. C21**
					Lot-I	**Lot-II**	**Lot-III@**		
				debossed "50" on one side and plain on other side.	biconvex, film coated tablets, debossed "50" on one side and plain on other side.	biconvex, film coated tablets, debossed "50" on one side and plain on other side.	biconvex, film coated tablets, debossed "50" on on e side and plain on other side.	debossed "50" on one side and plain on other side.	debossed "50" on one side and plain on other side.
			Average Weight (mg) [20 Tablets]	255.0 mg ± 3% (247.350 mg to 262.650 mg)	255.85 mg	256.15 mg	256.95 mg	256.75 mg	255.1 mg
			Group Weight of 20 Tablets	5.100 gm ± 3% (4.947 gm to 5.253 gm)	5.117 g	5.123 g	5.139 g	5.135 g	5.102 g
			Thickness (mm) [10 tablets]	4.5 ±0.3 mm 4.20 mm to 4.80 mm	4.45 – 4.55 mm	4.45 – 4.55 mm	4.47 – 4.58 mm	4.38 – 4.57 mm	4.45 – 4.55 mm
8.	Coating Yield		Reconciliation	NLT 96.0 % (Tentative)	99.26 %			99.34 %	97.06 %
			Actual Yield	NLT 96.0 % (Tentative)	99.29 %			99.40 %	98.96 %

2.7 Packaging:

S. No.	Process Parameter	Equipment ID	Critical variable	Acceptance Criteria	Observation		
					B. No. A21	B. No. B21	B. No. C21
					Machine MF/APM/03	Machine MF/APM/03	Machine MF/APM/02
1.	Packing	Blister Packing Machine MF/APM/03 MF/APM/02	Speed of machine	To be recorded	20 – 35 Strokes/Min.	22 - 25 Strokes/Min.	28 - 30 Strokes/Min.
			Sealing Temperature	To be recorded	170.0 – 200.0 ℃	191.0 – 194.3 ℃	194.6 – 196.1 ℃
			In-process parameters	As per BPR	Complies	Complies	Complies
			Actual Yield	NLT 94.50 %	99.66 %	99.46 %	98.73 %
			Batch Yield	To be recorded	99.85 %	99.90 %	99.13 %

Note: Batch process activity has been executed, verified, and recorded in respective batch manufacturing record.

3. Analytical Results:

3.1 LOD Results:

Sr. No	Test parameter	Specification limit	Sample location	Observation		
				B. No.: A21	**B. No.:** B21	**B.NO.** C21
1.0	LOD	NMT 1.00 % w/w	Top left	0.10 %	0.20 %	0.06 %
			Top Right	0.18 %	0.32 %	0.04 %
			Top Center	0.58 %	0.22 %	0.08 %
			Middle Right	0.28 %	0.30 %	0.08 %
			Middle left	0.30 %	0.16 %	0.10 %
			Bottom Center	0.40 %	0.12 %	0.08 %
			Composite	0.21 %	0.79 %	0.18 %

1.1 Analytical results of Lubricated Blend:

S. No.	Test parameter	Acceptance criteria	Location	Results (%)		
				B. No.: A21	**B. No.:** B21	**B.NO.** C21
1.0	Blend Uniformity	Average value should be between 95.0 % to 105.0 % of the labeled amount of Mirabegron	TBL	96.4	98.30	97.01
			TBR	101.1	96.97	106.77
			TFL	100.6	99.20	105.17
			TFR	101.2	104.67	106.26
			MC	97.2	98.83	104.72
			BBL	96.7	94.24	107.82
			BBR	98.7	95.41	105.63
			BFL	100.5	100.12	102.99
			BFR	102.9	96.17	102.03
			BC	97.5	100.84	100.99
Results (results reported in %)			**Min.**	**96.4**	**94.2**	**97.01**
			Max.	**102.9**	**104.7**	**107.82**
			Avg.	**99.3**	**98.5**	**103.94**
			% RSD	**2.26**	**3.07**	**3.12**

Remarks: Analytical data of blend uniformity sample at lubrication stage was found satisfactory and within the specification limits.

3.2 Analytical results of Lubricated Blend (Unloading):

S. No.	Test parameter	Acceptance criteria	Results (%)		
			B. No.: A21	**B. No.:** B21	**B.NO.**C21
1.0	Sieve analysis (Particle Size Distribution)				

1.1	30#	For Information	13.554 %	7.290 %	22.440 %
1.2	40#	For Information	44.040 %	44.523 %	37.367 %
1.3	60#	For Information	26.928 %	34.756 %	15.786 %
1.4	100#	For Information	5.897 %	5.233 %	4.755 %
2.0	Bulk Density	For Information	0.47 gm/ml	0.43 gm/ml	0.51 gm/ml
3.0	Tapped Density	For Information	0.54 gm/ml	0.50 gm/ml	0.61 gm/ml

Remarks: Analytical data of composite (Unloading) sample at lubrication stage was found satisfactory.

3.3 Analytical results of pre-compression:

S. No.	Test parameter	Acceptance criteria	Results (%)
			B. No.: A21
1.0	Dissolution		
1.1	3 Hrs.	NMT 65.0 %	**Min.** 30.3 % **Max.** 38.2 % **Avg.** 33.3 %
1.2	5 Hrs.	Between 40.0 – 90.0 %	**Min.** 54.7 % **Max.** 68.2 % **Avg.** 60.7 %
1.3	10 Hrs.	NLT 80.0 %	**Min.** 101.8 % **Max.** 108.3 % **Avg.** 104.7 %
2.0	Assay	90.0 to 110.0 % (For Information)	105.1 %

Remarks: Analytical data of pre-compression stage were found satisfactory and within the specification limits.

3.4 Low & high hardness challenge study of compression.

S. No.	Test parameter	Acceptance criteria	Results (%)	
			B. No.: A21	
			At low hardness	**At high hardness**
1.0	Dissolution			
1.1	3 Hrs.	NMT 65.0 %	**Min.** 24.2 % **Max.** 46.6 % **Avg.** 35.5 %	**Min.** 32.1 % **Max.** 43.9 % **Avg.** 37.6 %
1.2	5 Hrs.	Between 40.0 – 90.0 %	**Min.** 45.6 % **Max.** 78.9 % **Avg.** 60.8 %	**Min.** 59.1 % **Max.** 75.9 % **Avg.** 67.6 %
1.3	10 Hrs.	NLT 80.0 %	**Min.** 90.0 % **Max.** 107.9 % **Avg.** 103.8 %	**Min.** 104.0 % **Max.** 106.0 % **Avg.** 104.8 %

Remarks: Analytical data of Dissolution test at low & high hardness of compression stage were found satisfactory and within the specification limits.

3.5 Low & high-speed challenge study of compression.

S. No.	Test parameter	Acceptance criteria	**B. No.:** A21	
			At low speed	**At high speed**
1.0	Uniformity of weight	± 5.0 % of Average weight.	-1.6 % to 2.9 %	-2.6 % to 1.7 %

Remarks: Analytical data of Uniformity of weight at low & high speed of compression stage were found satisfactory and within the specification limits.

3.6 Start, Middle and end stage of compression.

S. No.	Test parameter	Acceptance criteria	**B. No.:** A21		
			At Stat	**At Middle**	**At end**
1.0	Uniformity of weight	± 5.0 % of Average weight.	-1.8 % to 1.9 %	-2.6 % to 2.5 %	-1.8 % to 1.7 %

Remarks: Analytical data of Uniformity of weight at start, middle & end of compression stage were found satisfactory and within the specification limits.

3.7 Start, Middle and end stage of compression.

S. No.	Test parameter	Acceptance criteria	**B. No.:** B21		
			At Stat	**At Middle**	**At end**
1.0	Uniformity of weight	± 5.0 % of Average weight.	-2.1 % to 1.8 %	-1.9 % to 2.8 %	-1.9 % to 2.1 %

Remarks: Analytical data of Uniformity of weight at start, middle & end of compression stage were found satisfactory and within the specification limits.

3.8 Start, Middle and end stage of compression.

S. No.	Test parameter	Acceptance criteria	B. No.: C21		
			At Stat	At Middle	At end
1.0	Uniformity of weight	± 5.0 % of Average weight.	-2.3 % to 4.0 %	-2.5 % to 3.9 %	-2.2 % to 3.9 %

Remarks: Analytical data of Uniformity of weight at start, middle & end of compression stage were found satisfactory and within the specification limits.

3.9 Compression composite.

S. No.	Test parameter	Acceptance criteria	Observation		
			B. No.: A21	B. No.: B21	B. No.: C21
1.0	Description	Oval shaped, white to slightly yellowish white, uncoated tablets, debossed "50" on one side and plain on other side.	Oval shaped, white to slightly yellowish white, uncoated tablets, debossed "50" on one side and plain on other side.	Oval shaped, white to slightly yellowish white, uncoated tablets, debossed "50" on one side and plain on other side.	Oval shaped, white to slightly yellowish white, uncoated tablets, debossed "50" on one side and plain on other side.
2.0	Average weight	250.0 mg ± 3.0 % w/w	251.980 mg	251.335 mg	255.030 mg

Remarks: Analytical data of compression composite were found satisfactory and within the specification limits.

3.10 Coating composite.

S. No.	Test parameter	Acceptance criteria	Observation		
			B. No.: A21	B. No.: B21	B. No.: C21
1.0	Description	Yellow coloured, oval shaped, biconvex, film coated tablets, debossed "50" on one side and plain on other side.	Yellow coloured, oval shaped, biconvex, film coated tablets, debossed "50" on one side and plain on other side.	Yellow coloured, oval shaped, biconvex, film coated tablets, debossed "50" on one side and plain on other side.	Yellow coloured, oval shaped, biconvex, film coated tablets, debossed "50" on one side and plain on other side.

2.0	Identification	The retention time of major peak in the chromatogram of test solution should be corresponds to that the standard solution obtained as directed in the assay.	The retention time of major peak in the chromatogram of test solution is corresponds to that the standard solution obtained as directed in the assay.	The retention time of major peak in the chromatogram of test solution is corresponds to that the standard solution obtained as directed in the assay.	The retention time of major peak in the chromatogram of test solution is corresponds to that the standard solution obtained as directed in the assay.
3.0	Thickness	4.5 ± 3.0 mm	4.48 to 4.56 mm	4.48 to 4.56 mm	4.45 to 4.57 mm
4.0	Length	12.0 mm ± 0.2 mm	11.96 to 11.98 mm	11.90 to 11.95 mm	11.95 to 12.05 mm
5.0	Width	6.0 mm ± 0.2 mm	5.97 to 6.00 mm	5.93 to 5.96 mm	5.98 to 6.05 mm
6.0	Avg. weight	255.0 mg ± 3.0 % w/w	256.290 mg	255.155 mg	252.785 mg
7.0	Uniformity of weight	± 5 % of Average weight	-2.8 % to 1.7 %	-2.6 % to 2.8 %	-3.6 % to 3.4 %
8.0	Related substan ces				
8.1	Single Maximum Impurity	NMT 0.5 %	0.08 %	0.03 %	0.04 %
8.2	Total Impurity	NMT 2.0 %	0.1 %	0.1 %	0.2 %
9.0	Assay	90.0 % to 110.0 %	96.9 %	99.8 %	102.7 %
10.0	Dissolution				
10.1	3 Hrs.	NMT 65.0 %	**Min.** 24.7 % **Max.** 29.4 % **Avg.** 27.3 %	**Min.** 21.8 % **Max.** 27.5 % **Avg.** 24.3 %	**Min.** 18.0 % **Max.** 33.7 % **Avg.** 27.8 %
10.2	5 Hrs.	Between 40.0 – 90.0 %	**Min.** 47.7 % **Max.** 57.6 % **Avg.** 52.4 %	**Min.** 45.5 % **Max.** 53.0 % **Avg.** 47.7 %	**Min.** 34.7 % **Max.** 63.2 % **Avg.** 54.7 %
10.3	10 Hrs.	NLT 80.0 %	**Min.** 95.8 % **Max.** 102.5 % **Avg.** 98.5 %	**Min.** 93.3 % **Max.** 98.8 % **Avg.** 95.4 %	**Min.** 77.7% **Max.** 108.6 % **Avg.** 103.9 %
11.0	Residual solvent				
11.1	Isopropyl alcohol	NMT 5000 PPM	BDL (LOD=92.74 ppm)	BDL (LOD=92.74 ppm)	Below LOD

Remarks: Analytical data of coating stage were found satisfactory and within the specification limits.

3.11 Packing (Worst case) Results:

S. No.	Test parameter	Acceptance criteria	Observation
			B. No.: A21
1.0	Assay	90.0 to 110.0 % of labeled amount.	102.1 %
2.0	Related substances		
2.1	Single Maximum Impurity	NMT 0.5 %	0.08 %
2.2	Total Impurity	NMT 2.0 %	0.1 %

Remarks: Analytical data of packing (worst case) were found satisfactory and within the specification limits.

3.12 Finished Product Analytical Results:

S. No.	Test parameter	Acceptance criteria	Finished Product s Result		
			B. No.: A21	**B. No.:** B21	**B. No.:** C21
1.0	Description	Yellow coloured, oval shaped, biconvex, film coated tablets, debossed "50" on one side and plain on other side.	Yellow coloured, oval shaped, biconvex, film coated tablets, debossed "50" on one side and plain on other side.	Yellow coloured, oval shaped, biconvex, film coated tablets, debossed "50" on one side and plain on other side.	Yellow coloured, oval shaped, biconvex, film coated tablets, debossed "50" on one side and plain on other side.
2.0	Identification	The retention time of major peak in the chromatogram of test solution should be corresponds to that the standard solution obtained as directed in the assay.	The retention time of major peak in the chromatogram of test solution is corresponds to that the standard solution obtained as directed in the assay.	The retention time of major peak in the chromatogram of test solution is corresponds to that the standard solution obtained as directed in the assay.	The retention time of major peak in the chromatogram of test solution is corresponds to that the standard solution obtained as directed in the assay.
3.0	Thickness	4.5 ± 3.0 mm	4.48 to 4.56 mm	4.48 to 4.56 mm	4.45 to 4.57 mm
4.0	Length	12.0 mm ± 0.2 mm	11.96 to 11.98 mm	11.90 to 11.95 mm	11.95 to 12.05 mm
5.0	Width	6.0 mm ± 0.2 mm	5.97 to 6.00 mm	5.93 to 5.96 mm	5.98 to 6.05 mm
6.0	Average weight	255.0 mg ± 3.0 % w/w	256.290 mg	255.155 mg	252.785 mg
7.0	Uniformity of weight	NMT 2 tablets in 20 deviates from the average weight by more than 5.0 %. No tablet deviates from the average weight by more than 10.0 %.	Deviation: -2.8 % to 1.7 %	Deviation: -2.6 % to 2.8 %	Deviation: -3.6 % to 3.4 %
S. No.	**Test parameter**	**Acceptance criteria**	**Finished Product Results**		
			B. No.: A21	**B. No.:** B21	**B. No.:** C21
8.0	Related substances				
8.1	Single Maximum Impurity	NMT 0.5 %	0.08 %	0.03 %	0.04 %
8.2	Total Impurity	NMT 2.0 %	0.1 %	0.1 %	0.2 %
9.0	Assay	90.0 % to 110.0 %	96.9 %	99.8 %	102.7 %
10.0	Dissolution				
10.1	3 Hrs.	NMT 65.0 %	**Min.** 24.7 % **Max.** 29.4 % **Avg.** 27.3 %	**Min.** 21.8 % **Max.** 27.5 % **Avg.** 24.3 %	**Min.** 18.0 % **Max.** 33.7 % **Avg.** 27.8 %

10.2	5 Hrs.	Between 40.0 – 90.0 %	**Min.** 47.7 % **Max.** 57.6 % **Avg.** 52.4 %	**Min.** 45.5 % **Max.** 53.0 % **Avg.** 17.7 %	**Min.** 34.7 % **Max.** 63.2 % **Avg.** 54.7 %
10.3	10 Hrs.	NLT 80.0 %	**Min.** 95.8 % **Max.** 102.5 % **Avg.** 98.5 %	**Min.** 93.3 % **Max.** 98.8 % **Avg.** 95.4 %	**Min.** 77.7% **Max.** 108.6 % **Avg.** 103.9 %
11.0	Residual solvent				
11.1	Isopropyl alcohol	NMT 5000 PPM	BDL (LOD=92.74 ppm)	Below LOD	Below LOD
12.0	Microbial Limit Te st				
12.1	Total Aerobic viable Count	NMT 1000 cfu/gm	30 cfu/g	30 cfu/g	30 cfu/g
12.2	Total molds and yeasts count	NMT 100 cfu/gm	Less than 10 cfu/g	Less than 10 cfu/g	Less than 10 cfu/g
12.3	E. coli	Should be absent 1 gm	Absent/g	Absent/g	Absent/g

4. Conclusion :

The validation batches of Mirabegron Tablets 50 mg were manufactured as per approved Batch manufacturing Record. All required validation activities were completed, and results are compiled in this report. During validation study critical process parameters were monitored as All the In-process test parameters were found well within the specified limit. There is no change in method of manufacturing followed during manufacturing of all these validation batches. No anomaly was noted with respect to the testing parameters of all these batches when tested using the approved specification. This interim validation report proves that the manufacturing process of Mirabegron Tablets 50 mg and is consistent and meets the predetermined specifications and required quality attributes and based on the interim report this batch can be release for marketing and distribution.

5. References:

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