



A Process Development and Validation of Mirabegron Extended Release 25 Mg and Silodosin 8mg Bilayer Tablet

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ABSTRACT:

Introduction: Mirabegron & silodosin, is used often in combination as bilayer tablets, are primarily used to treat the symptoms of overactive bladder (OAB) & benign prostatic hyperplasia (BPH). Mirabegron drug helps to relax bladder muscles by increasing urine storage capacity and reduction in urine urgency. The drug Silodosin helps to relax the muscles in the prostate and bladder neck by improving urinary flow and reducing BPH-related symptoms. The aim of the research study is to process validation (PV) of the formulation development of bilayer tablet of Mirabegron & silodosin drug. Process validation batches were manufactured for the demonstration of the process performance for reproducibility and consistency within its range of operation as per process design. Mirabegron to be manufactured in extended-release form for prolonged action and silodosin in immediate release form. Based on the results of the validation process, the observed results indicate that the process design for the manufacturing of the product, mirabegron and silodosin tablet 25mg & 8 mg is found to be robust enough for manufacturing of a quality drug product. These validated products give the specified quality attribute results & meet all the predetermined specification criteria. The PV study highlights the potential of a Mirabegron ER & Silodosin bilayer tablet approach, combining immediate release & Extended-release formulation, for creating an extended-release dosage form mirabegron & immediate release dosage form of silodosin.

Objectives: The main objective of Process validation of Mirabegron 25 mg (ER) & Silodosin 8 mg Tablets is for attain the critical quality attributes within the specified limit and to validate the process parameters as per the quality standards.

Objectives of bilayer tablets:

- ❖ It is possible to integrate one or two distinct active medicinal substances.
- ❖ Additionally, they are employed to separate incompatible active medicinal components.
- ❖ By sandwiching, the API layer's surface area is altered. One or two inactive layers can regulate it and cause it to reach the erodible or swellable barriers for modified release.
- ❖ It is employed to fix a mixture of various active medicinal components. The drug product's life cycle is extended.

Methods: The formulations are designed for bilayer tablets combining IR (immediate release) and ER (Extended release) components in different ratios. Each drug layer has its separate granulation procedure. For the preparation of Immediate Release (IR) granules, Silodosin, microcrystalline cellulose, lactose monohydrate, and SSG (sodium starch glycolate) were mixed with an inactive binding solution, which is povidone-



90 dissolved in purified water, using a high-speed mechanical stirrer. After mixing solutions in dry powder, the wet granules were dried using an FBD. Dried granules were further sized using the 1.0 mm mesh and lubricated with magnesium stearate and Aerosil/colloidal silicon dioxide. For the preparation of SR granules, mirabegron, lactose, starch and HPMC K4 passed through the sieve and further binding done by using PVPK-90. The dry powder was mixed in RMG, and further binding has been done by the binding agent and dried by using FBD 120 kg. Dried granules sized by 1.0 mm mesh and mixed using Double cone Blender 185 ltr capacity. After mixing, the granules were lubricated with magnesium stearate (Jadiya et al., 2024). The both layer granules were further compressed to form the bilayer tablets consisting of Immediate Release and Sustained release layers using an Cadpress IV compression machine using the round shape plain punches. The compaction pressure was set at 10 kN, to achieve the required hardness of tablets during the process of compression. The batch size was 2.0 lac tablets. After forming the bilayer tablets, the tablets were further coated with Opadry coating material using a solace auto coater 37" capacity.

Results: The all physical and chemical analysis results are evaluated as per the protocol and parameters

Conclusions: Based on summary report and observed result at different stage, it is concluded that process validation of Mirabegron 25 mg (ER) & Silodosin 8 mg Tablets was carried out as per respective protocol and observed results of critical process parameters and critical quality attributes were found within the specified limit. Finished product results of batch were found within the specified limit.

1. Introduction

Bilayer tablets continue to represent a new era in which controlled delivery design can be effectively advanced laterally through a variety of methods to provide an approach to an effective drug transport system (Han et al., 2022). Bi-layer tablets appear to be designed for the simultaneous release of two drugs, two discordant constituents, and then similarly for sustained release tablets, where the maintenance dose is the second layer and the immediate release is the first layer. Bilayer tablets continue to be an improved, advantageous way to overcome the shortcomings of single-layered tablets (Maddiboyina et al., 2020).

The concept of validation has undergone constant development since it was originally introduced in the US in 1978. The idea of validation has grown over time to include a variety of tasks, from computerized systems for clinical trials to analytical techniques used for quality control of pharmacological ingredients and items. Because each process is so different, there is one-size-fits all method for validation and regulatory agencies like the FDA and

EC have created broad optional standards (Ishitsubo et al., 2024).

Nevertheless, validation is one component of quality assurance related to a specific process. The term validation simply implies "action of proving effectiveness" or "assessment of validity." Validation, as defined by the European Community for pharmaceutical products, is the "action of proving" that any procedure, process, requirement, material, activity, or system genuinely produces the desired results in line with GMP principles. A documented procedure that offers a high level of assurance that a particular process will reliably yield a product that satisfies its predefined specifications and quality attributes is known as process validation (Swetanshu et al., 2020).

Mirabegron (Mrb), a β_3 -adrenoceptor agonist, was a new class of pharmaceutical treatment for OAB. The mechanism of action differences suggest that adding a β_3 -adrenoceptor agonist to an antimuscarinic agent could enhance efficacy in the treatment of OAB (Lee et al., 2019). The European urology association guideline recommends α -1-blockers for distal ureteric stones.



Tamsulosin and silodosin are the most commonly used alpha-1-blockers in medical expulsive therapy. Silodosin has a 38-fold higher selectivity for α -1A than tamsulosin. In a study by Gupta et al, tamsulosin and silodosin had expulsion rates of 58% and 82%, respectively. Silodosin was also associated with a shorter expulsion time compared to tamsulosin. In the opposite way of thinking, ureter relaxation may be helpful for easy F-URS procedure, and this can easily be achieved by administering silodosin preoperatively (Diab et al., 2024).

2. Objectives

2.1 Formulation Development:

- 2.1 To design a bilayer tablet formulation that combines **Mirabegron (Extended Release)** and **Silodosin (Immediate Release)**, utilizing appropriate excipients for each drug to optimize their release profiles.
- 2.2 To select suitable polymers for the **extended-release (ER)** layer of **Mirabegron** and disintegrants for the **immediate-release (IR)** layer of **Silodosin**.

3. Preformulation Studies:

- 3.1 To assess the physicochemical properties of **Mirabegron** and **Silodosin**, including solubility, particle size, and compatibility with selected excipients.
- 3.2 To perform compatibility studies using techniques like **FTIR** and **DSC** to ensure no adverse interactions between the drugs and excipients.

4. Optimization of Drug Release:

- 4.1 To optimize the formulation of the bilayer tablet using **Design of Experiments (DOE)** methodology, focusing on critical factors such as excipient concentration, compression force, and drug release characteristics.
- 4.2 To determine the ideal release profile for both drugs, ensuring **Mirabegron** provides sustained release and **Silodosin** offers immediate release.

5. Evaluation of Tablet Properties:

- 5.1 To assess the physical characteristics of the bilayer tablets, including weight variation,

hardness, friability, thickness, and interlayer adhesion.

- 5.2 To conduct in vitro dissolution testing to evaluate the release profiles of both drugs, and to ensure that the **IR layer** (Silodosin) achieves rapid drug release, while the **ER layer** (Mirabegron) provides sustained drug release over 24 hours.

6. Stability Testing:

- 6.1 To perform stability studies under **long-term** and **accelerated conditions** to assess the physical, chemical, and pharmacological stability of the bilayer tablets.
- 6.2 To evaluate the impact of packaging materials on the stability of the tablets, particularly in terms of moisture sensitivity and shelf life.

3. Methods

3.1 Preparation of Bilayer Tablet

The formulations are designed for bilayer tablets combining IR (immediate release) and ER (Extended release) components in different ratios. Each drug layer has its separate granulation procedure. For the preparation of Immediate Release (IR) granules, Silodosin, microcrystalline cellulose, lactose monohydrate, and SSG (sodium starch glycolate) were mixed with an inactive binding solution, which is povidone-90 dissolved in purified water, using a high-speed mechanical stirrer. After mixing solutions in dry powder, the wet granules were dried using an FBD. Dried granules were further sized using the 1.0 mm mesh and lubricated with magnesium stearate and Aerosil/colloidal silicon dioxide. For the preparation of SR granules, mirabegron, lactose, starch and HPMC K4 passed through the sieve and further binding done by using PVPK-90. The dry powder was mixed in RMG, and further binding has been done by the binding agent and dried by using FBD 120 kg. Dried granules sized by 1.0 mm mesh and mixed using Double cone Blender 185 ltr capacity. After mixing, the granules were lubricated with magnesium stearate (Jadaya et al., 2024). The both layer granules were further compressed to form the bilayer tablets consisting of Immediate Release and Sustained release layers using an Cadpress IV compression



machine using the round shape plain punches. The compaction pressure was set at 10 kN, to achieve the required hardness of tablets during the process of compression. The batch size was 2.0 lac tablets. After forming the bilayer tablets, the tablets were further coated with Opa dry coating material using a solace auto coater 37" capacity.

Table1. Composition of formulations for bilayer tablet Mirabegron ER and Silodosin.

Sr. No.	Name of Raw Materials	Qty./Tablets (mg)	Qty./Batch (Kg)
Mirabegron Layer			
1.	Mirabegron	25.38	5.076
2.	Lactose	124.12	24.824
3.	Starch	33.75	6.750
4.	H.P.M.C. (K-4M)	32	6.400
5.	Isopropyl Alcohol	85 ml	17.000 Ltr
6.	Povidone K-90	3	0.600
7.	Colloidal Silicon Dioxide	2.25	0.450
8.	Magnesium Stearate	IP	0.900

Silodosin Part			
1.	Silodosin	8.44	1.688
2.	Lactose	70.85	14.17
3.	Microcrystalline Cellulose	32.53	6.506
4.	Sod starch glycollate	2.5	0.5
5.	Colour Iron Oxide Red	0.04	0.008
6.	Purified Water	25	5
7.	Povidone K-90	1.88	0.376
8.	Colloidal Silicon Dioxide	1.25	0.25
9.	H.P.M.C. E3	3.13	0.626
10.	Magnesium Stearate	1.88	0.376
11.	Sod. starch	2.5	0.5

glycollate			
Coating materials			
12.	Opadry red	8.75	1.750
13.	Purified water	50	10 ltr

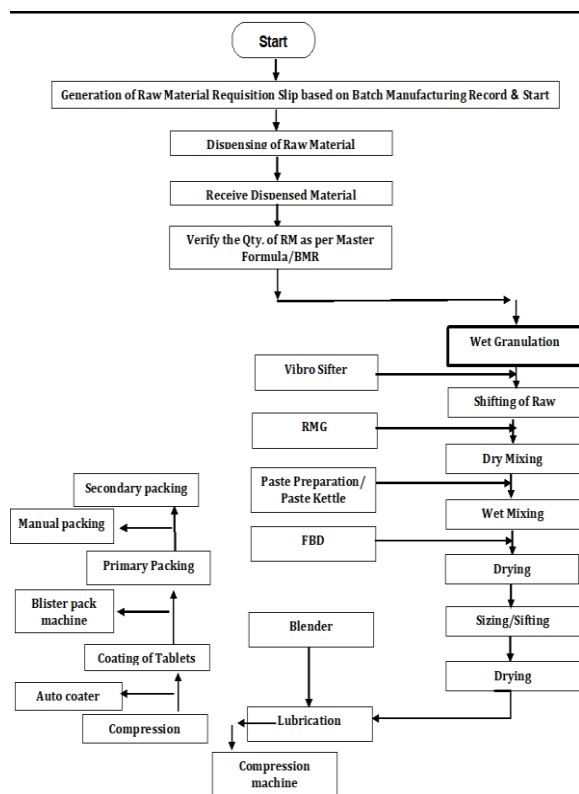
3.2 Selection of Manufacturing Equipment: The equipment for the manufacturing of the products has been selected based on the equipment capacity & design. The equipment's used for the manufacturing of bilayer products has been selected on the basis of manufacturing process design, product batch size, and available and required utility assessment criteria. The list of equipment has been approved based on the manufacturing process of the product Mirabegron Extended Release 25 Mg and Silodosin 8mg Tablet (Bilayer Tablets).

Table2: Details of Equipment's Used for the Manufacturing of Batches

Sr. No.	Equipment Name	Capacity	Make
1	Vibro Sifter	30 Inches	Tapasya
2	RMG	120 ltrs.	Tapasya
3	Multi-mill	---	Avon
4	FBD	120 kg	Solace
5	Double Cone Blender	185 L	Tapasya
6	Tablet Compression Machine	45 Stations Bilayer	Cadmach IV
7	Metal Detector	NA	Technofour
8	Vibro Duster	NA	Technofour
9	Auto coater	37"	Solace
10	Colloid mill	10 ltrs	Tapasya
11	Blister Packing Machine	40 -60 cuts/min	Paam
12	Weighing Balance	200 g	Metler Toledo
13	Weighing Balance	150 Kg	Metler Toledo



Figure 1: Flow chart of manufacturing & packaging process:



3.3 Process Validation of Mirabegron (ER) and Silodosin Bilayer Tablet: Various quality and control evaluation parameters were performed for the evaluation of bilayer table formulation. Table 3 described in detail about manufacturing process, process variables and measuring controls.

Table 3: Product Critical Quality Attributes, Risk & control evaluation:

Manufacturing Process	Process Variables	Process Measuring Controls
Initial & Final Sifting	Granules size	Sieve Integrity
Dry Granulation & Wet Granulation	RMG Occupancy Rpm Impeller Rpm Chopper Amperage	Content Uniformity

	Mixing Time	
Semi Drying/ Final Drying	Inlet Temperature Outlet Temperature Bed Temperature Drying Time	Drying Time Lod Of Granules
Lubrication	Rpm Time	Assay BulkDensity ParticleSizeDistribution
Compression	MachineRpm HopperLevel LubricationOf Machines Compaction Force	Tablet Appearance UniformityOfWeight DisintegrationTime Hardness Of Tab Thickness Of Tab Friability % %AssayCu
Coating	SprayRate CoatingPanRpm BedTemperature Inlet Temperature Bed Temperature	Tablet Description % Weight Gain Physical Parameter Assay
Packing	Forming & Sealing Temperature Machine Rpm	Leak Test Knurling FinishedProductQuality Attribute

7. Discussion

As per the process validation protocol, sampling of products has been carried out in different stages of manufacturing, i.e. granulation, compression, coating & finished stage. The samples are further analyzed as per the specification of evaluation parameters of formulation process of bilayer tablet. The sampling plan of product was mentioned in the approved validation protocol accordingly sampling has been done. The



analytical result of the product gives assurance that manufacturing processes are well-validated. Product sampling and analytical results of all the validation batches discussed in the below sections.

Pre-Formulation and Evaluation of Bilayer Tablet: The analytical results of the formulation development process of bilayer tablet Mirabegron (ER) 25 mg and Silodosin 08 mg were observed in dry mixing stage. Sample was collected from three stages of the mixer i.e. top, middle and bottom. Detailed analytical reports of the samples were shown in table 4& 5.

Table 4: Analytical Results of Mirabegron (ER) in dry Mixing Stage

Sampling Point	Parameters	Acceptance Criteria	Observed Results		
			Trial 1	Trial 2	Trial 3
Top (L1)	Description	white coloured granular powder.	Complies	Complies	Complies
	Mirabegron EP2 5 mg	98.0 % to 110.0% of labeled amount	103.2 %	98.8%	102.3%
Middle (L2)	Description	white coloured granular powder.	Complies	Complies	Complies
	Mirabegron EP2 5 mg	98.0 % to 110.0% of labeled amount	100.3 %	102.5%	101.0%
Bottom (L3)	Description	white coloured granular powder.	Complies	Complies	Complies
	Mirabegron	98.0 % to 110.0% of labeled	103.5 %	101.7%	98.1%

Sampling Point	Parameters	Acceptance Criteria	Observed Results		
			Trial 1	Trial 2	Trial 3
Composite	EP2 5 mg	amount			
	Description	white coloured granular powder.	Complies	Complies	Complies
Composite	Mirabegron EP2 5 mg	98.0 % to 110.0% of labeled amount	98.9%	104.7%	100.6%

Table 5: Analytical Results of Silodosin in dry Mixing Stage

Sampling Point	Parameters	Acceptance Criteria	Observed Results		
			Trial 1	Trial 2	Trial 3
Top (L1)	Description	light pink coloured granular powder	Complies	Complies	Complies
	Silodosin JP08 mg	98.0 % to 110.0% of labeled amount	103.2%	101.8%	105.5%
Middle (L2)	Description	light pink coloured granular powder	Complies	Complies	Complies
	Silodosin JP 08 mg	98.0 % to 110.0% of labeled amount	100.3%	98.6%	98.8%



Sampling Point	Parameters	Acceptance Criteria	Observed Results		
			Trial 1	Trial 2	Trial 3
Bottom (L3)	Description	light pink coloured granular powder	Complies	Complies	Complies
	Silodosin JP 08 mg	98.0 % to 110.0% of labeled amount	103.5%	98.5%	98.4%
Compo site	Description	light pink coloured granular powder	Complies	Complies	Complies
	Silodosin JP 08 mg	98.0 % to 110.0% of labeled amount	102.3%	105.8%	98.6%

Formulation and Evaluation of Coated Tablet:

Evaluation process was done for the final coated bilayer tablet of Mirabegron 25 mg and Silodosin 08 mg through various parameters like description, identification, average weight, uniformity of weight and dissolution. The detailed evaluation values of the all parameters are show in table 6.

Table 6: Analytical results of coated tablets.

Uniformity of weight	Not more than 2 tablets in 20 deviates from the average weight by more than 5.0%. No tablet	Deviation - 3.79 to +1.59%	Deviation - 1.70 to +2.17%	Deviation - 2.37 to +4.04 %

	deviates from the average weight by more than 10.0%.				
Dissolution					
1 st hour Mirabegron EP	Not more than 30.0 % of Labeled amount	Minimum	8.5%	12.5%	18.4%
		Maximum	12.2%	15.7%	22.5%
		Average	11.1%	14.0%	20.4%

10 hour	Not less than 75.0% of labeled amount	Minimum	80.0%	85.7%	90.5%
		Maximum	98.8%	96.2%	98.8%
		Average	90.7%	90.6%	93.8%
Silodosin JP	Not less than 70% (Q) of Labeled amount in 45 minutes	Minimum	85.3%	92.3%	92.2%
		Maximum	95.3%	95.6%	99.1%
		Average	90.3%	93.9%	96.3%

Uniformity of Dosage units (By content Uniformity)

Mirabegron EP	Acceptance value should be less than 15	9.10	11.2	5.50
Silodosin JP	Acceptance value should be less than 15	10.30	13.0	5.49
Assay: Each Film coated tablet contains:				
Mirabegron	90.0 to 110.0% of labeled amount	103.0 %	103.4%	102.5 %



ron EP (as extended release form) 25 mg					
Silodosin JP... 8 mg	90.0 to 110.0% of labeled amount	98.4%	98.1%	98.3%	

Formulation and Evaluation of Final Bilayer Tablet:

Formulation of the bilayer tablet of Mirabegron 25 mg and Silodosin 08 mg was done with the help of standard operating procedure. The evaluation of the formulation process was done for the final compressed bilayer tablet of Mirabegron 25 mg and Silodosin 08 mg compositions. The detailed evaluation values of the all parameters are show in table 7.

1 st hour Mirabegron EP	Not more than 30.0 % of labeled amount.	Minimum	8.5%	12.5 %	18.4 %
		Maximum	12.2 %	15.7 %	22.5 %
		Optimum	11.1 %	14.0 %	20.4 %
3 rd hour Mirabegron EP	25.0 to 65.0 % of labeled amount	Minimum	32.3 %	38.1 %	42.1 %
		Maximum	38.9 %	44.4 %	47.0 %
		Optimum	35.1 %	40.4 %	45.9 %

10 hour Mirabegron EP	Not less than 75.0 % of labeled amount	Minimum	80.00 %	85.70 %	90.50%
		Maximum	98.80 %	96.20 %	98.80%
		Optimum	90.70 %	90.60 %	93.80%
Silodosin JP	Not less than 70% (Q) of Labeled amount in 45 minutes	Minimum	85.30 %	92.30 %	92.20%
		Maximum	95.30 %	95.60 %	99.10%
		Optimum	90.30 %	93.90 %	96.30%

Uniformity of Dosage units (By content Uniformity)

Mirabegron EP	Acceptance value should be less than 15	9.1	11.2	5.5
Silodosin JP	Acceptance value should be less than 15	10.3	13	5.49

Assay: Each Film coated Bilayer tablet contains:

Mirabegron EP (as extended-release form) 50 mg	90.0 to 110.0% of labelled amount	103.00 %	103.40%	102.50%
Silodosin JP 8 mg	90.0 to 110.0% of labelled amount	98.40 %	98.10%	98.30%

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