



## Original Research Article

## Process validation of prasugrel hydrochloride tablet USP

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## ABSTRACT

Process validation is an essential part for the safety and quality of the drug products. Validation act as guidance that is intended to assist manufacturers in understanding quality management system requirements concerning process validation. It is a fundamental component for assuring the quality system used by pharmaceutical industries. Process validation is the key element to ensure the identity, purity, safety, and efficacy of drug products. The process validation of Prasugrel Hydrochloride Tablet USP precisely focused on the aim and method of analysis. The emphasis will be on the practical inspectional requirement, rather than on a theoretical approach that does not reflect the practicalities encountered when validating actual production operations. The Process validation reduces product recalls and troubleshooting assignments which results in more economical manufacturing process and quality products. In this paper an overview is given on process validation with special reference to solid dosage form of Prasugrel Hydrochloride Tablet USP containing dose of 10 mg.

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1. Introduction<sup>1-17</sup>

Process validation establishes the flexibility and constraints in the manufacturing process controls to attain the desirable attributes in the drug product while preventing undesirable properties.

This is an important concept, because of support and define the validation, which is a systematic approach to identifying, measuring, evaluating, documenting, and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product. Validation therefore challenges the adequacy and reliability of a system or process to meet predetermined criteria on a consistent basis from batch to batch.

The primary objective of process validation is; to provide a high degree of assurance of quality, to ensure the consistency of the manufacturing operation and reproducibility, to demonstrate the robustness of the process and to ensure the existence of all necessary quality

assurance system within organization.

The field of validation is divided into a number of subsections includes Process validation, Cleaning validation, Equipment validation, Validation of analytical methods.

Process validation includes a series of processing activities carried out over the lifecycle of final product categorized as

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

2. Drug Review<sup>18-20</sup>

## 2.1. Pharmacopoeial description

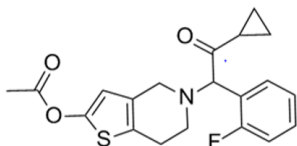
1. Molecular Formula- C<sub>20</sub>H<sub>20</sub>FNO<sub>3</sub>S.
2. IUPAC Name- 5- [2- cyclopropyl -1- (2-fluorophenyl) -2- oxoethyl] -4, 5, 6, 7- tetrahydrothieno [3, 2 -c] pyridin-2-yl acetate.

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3. Molecular Weight- 373 44100g/mol g mol-1.

## 2.2. Structure



## 2.3. Pharmacokinetic parameters

1. Bioavailability in the tablet form- >50%.
2. Protein binding- 94-98%.
3. Metabolism- Hepatic.
4. Half life- 7- 8 hours.
5. Excretion – 50% renal, 46% biliary.

## 2.4. Pharmacological actions of prasugrel

1. Prevention of thrombosis used in combination with low dose aspirin.
2. Acute coronary syndrome without ST-segment elevation.
3. Prevention of vascular ischemic events in patients with symptomatic atherosclerosis.

## 2.5. Adverse drug reaction

1. CVS- Hypertension (8%), Hypotension (4%), Bradycardia and Peripheral edema (3%).
2. CNS-Headache (6%), Dizziness (4%), Fever and Extremity pain (3%).
3. Dermatologic rash (3%).
4. Gastrointestinal Haemorrhage.
5. Thrombotic Thrombocytopenic purpura.
6. Severe Neutropenia (low white blood cell).
7. Use of non-steroidal anti-inflammatory drugs is discouraged in those taking prasugrel due to increased risk of digestive tract haemorrhage.

Most studies researching Prasugrel do not compare patients on Prasugrel to patients taking placebo; rather Prasugrel use is compared with use of aspirin. Thus attributing side effects directly to prasugrel is difficult. Other gastrointestinal side effect includes, Diarrhea, Rash Respiratory, Upper GI discomfort, Gastric or duodenal ulcer, gastritis, Upper respiratory infections, rhinitis, shortness of breath, cough.

## 3. Plan of Work

### 3.1. Literature survey<sup>21-35</sup>

### 3.2. Selection of Formulation Selection of formulation and preparation of drug/excipient profile

Prasugrel Hydrochloride tablets USP 10 mg were selected for the process validation. Drug profile was prepared

for formulation and it included the chemical data, pharmacokinetic data and therapeutic consideration. Each excipients used in the formulation was described for their physical properties, solubility, pH, storage and also their functional category.

### 3.3. Selection of type of process validation and preparation of validation protocol

Process validation was selected for that three consecutive batches were taken or selected.

### 3.4. Analysis of sample as per specification

Various tests were carried out as per specification mentioned in protocol after collecting the sample. Results of the entire test were prepared.

### 3.5. Review and compilation of results

Review and compilation of all three batches had done. Submission of final discussion and reports, deviation, summary and conclusion of any observation was included.

## 4. Material and Methods

All the equipment's and instruments must be calibrated before use. These are Equipments/Instruments Details: Sifter (300-500 Kg/Hour), Multi mill (50 to 250 Kg/Hour), RMG (400 Liters), FBD (150 Kg), Octagonal Blender (1200 lit), Compression Machine (27 station), Auto Coater(150 kg), Blister Packaging(200 blister/min), Paste Kettle(50 Liters), Metal Detector, Electronic Balance (60kg), Disintegration Apparatus, Vernier Caliper(6 inch), Leak test Apparatus, Friability Tester and Hardness Tester.

By using these above mentioned equipments and instruments manufacturing flow chart has followed and data filled under the validation protocol which includes 21 parameters; Pre-Approval, Purpose, Objective, Scope, Responsibility, Type of Process Validation, Training, Validation Strategy, Document Verification, Product Information, Manufacturing Formula, Manufacturing Process Flow Diagram, Manufacturing Procedure, Sampling Plan, Sampling Locations, Preparation of a Validation Protocol, Reference Documents, Deviations & change control (if any), Summary & Conclusion, Abbreviations and Protocol Post Approval.

## 5. Excipients profile

### 5.1. Dibasic calcium phosphate

Chemical name: Calcium monohydrogen Phosphate (1:1)  
 Chemical formula: CaHPO<sub>4</sub> Physical state and appearance: Powdered solid  
 Odour: Odourless  
 Colour: White

Functional Category: Dietary supplement

### 5.2. Aerosil 200

Chemical name: Silicon Dioxide

Chemical formula:  $\text{SiO}_2$  Physical state and appearance: Powdered solid

Odour: Odourless

Taste: Tasteless

Colour: White

Functional Category: Anticaking agent, improve tablet properties such as hardness, friability.

### 5.3. Lactose

Chemical formula:  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$  Physical state and appearance: white crystalline powder

Odour: Odourless

Functional Category: Filler

### 5.4. Starch

Molecular formula:  $(\text{C}_6\text{H}_{10}\text{O}_5)_n$

Physical state and appearance: White amorphous powder.

Odour: Odourless

Functional Category: Food additive, binder

### 5.5. Sorbitol solution (70%)

Physical state and appearance: Liquid

Colour: Clear Colorless

Solubility: Easily soluble

Functional Category: Hyperosmotic laxative

### 5.6. Talc

Chemical formula:  $3\text{MgO} \cdot 4\text{SiO}_2 \cdot \text{H}_2\text{O}$

Physical state and appearance: Powdered solid

Odour: Odourless

Colour: White, Greyish white

Solubility: Insoluble in water

Functional Category: Glidant

### 5.7. Magnesium stearate

Chemical formula:  $(\text{C}_{17}\text{H}_{35}\text{COO})_2\text{Mg}$

Physical state and appearance: Solid

Solubility: Very slightly soluble in cold water

Functional Category: Antiadherent, lubricant

## 6. Experimental Work

Evaluation parameters of tablet are as follows:

### 6.1. Content uniformity

After the compression method the content uniformity of tablets was tested. The assay method was followed to check

the content uniformity.

### 6.2. Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

### 6.3. Hardness

The crushing strength  $\text{Kg/cm}^2$  of prepared tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester. The average hardness and standard deviation was determined.

### 6.4. Thickness

Twenty tablets were randomly selected from each batch and thickness was measured by using Digital Vernier Caliper.

### 6.5. Friability

Twenty tablets were weighed and placed in the Roche friability testing apparatus and apparatus was rotated at 100 rpm. After revolutions the tablets were deducted and weighed again. Difference in initial and final weight determines friability.

### 6.6. Dissolution test

Dissolution test were carried out to determine the amount of drug released during a specific period of time using USP apparatus-I. 5ml of sample was withdrawn after specified time interval, and was replaced by an equal volume of fresh dissolution medium to maintain the sink condition. Collected samples were analyzed spectrophotometrically.

### 6.7. Disintegration test

Six tablets from each batch were utilized for disintegration studies in distilled water at  $37^\circ\text{C}$  using a Disintegration Apparatus USP STD. The disintegration time was taken to be the time no granule of any tablet was left on the mesh of the apparatus.

## 7. Process Validation Includes Various Critical Process Parameters and Specifications

## 8. Packing

### 8.1. Process parameters

1. Area Temp - NMT  $25^\circ\text{C}$  & RH-NMT 55%.
2. Description of Pack.
3. Sealing quality- Sealing roller Temp ( $170\text{-}190^\circ\text{C}$ ).
4. Number of tablets in pack (count).
5. Leak Test (For 10's).
6. Attachment: Pack Style 10's.

**Table 1:** Critical process parameters

Process	Equipment	Manufacturing Process Parameter
Sifting	Sieve used for Sifting	20#, 40# sieve; Area temp-NMT 25°C
Dry Mixing	RMG	Slow speed- 15 min; Fast speed- 5 min.
Binder Preparation	S.S. container	Cool the paste up to 50°C -60°C.
Wet Mixing	RMG with impeller	Slow speed for 10 minutes.
Drying	FBD bowl	Fluidize for 15 min. Inlet temp 55-60°C.
Rasping and Sizing	Multi Mill	2.5 mm screen with knives. Resifted through 16 # in mechanical sifter.
Blending & Lubrication	Blender	Blend 15 min. & Lubricate for 5 minutes at slow speed.
Compression	Compression Machine	Machine speed: 1200 TPM (27 Stations)
Coating	Auto Coater	Preheat temp: 30 - 35°C In let temperature: 40 - 45°C Out let temperature: 35 - 40°C Bed temperature : 30 - 40°C Pan RPM: 2 - 5 rpm

**Table 2:** Finished product specifications

S No.	Test	Specifications
1.	Description	Yellowish beige colour, oval shaped, film coated tablets with logo engraved on one side and plain on other side.
2.	Identification (BY HPLC)	The retention time of major peak obtained in test solution should correspond to that obtained in the chromatogram of the standard solution in the assay.
3.	Average weight	310.0 mg $\pm$ 2.0%
4.	Thickness	4.4 mm $\pm$ 0.2 mm
5.	Uniformity of Dosage units	The acceptance value (AV) for 10 units should be less than or equal to 15.0
6.	Disintegration Time	Not more than 30 minutes
7.	Dissolution (By HPLC)	NLT 70.0% of the labeled amount of Prasugrel hydrochloride is dissolved in 30 minutes.
8.	Assay (% Label Claim): Prasugrel hydrochloride Content Claim: 10 mg/tablet (5% overages)	NLT 97.0% and NMT 110.0% of the labelled amount of Prasugrel hydrochloride

## 8.2. Sampling location

Samples were taken from the packing belt.

## 9. Sampling Plan and Testing

### 9.1. Sampling interval

Samples were taken at initial, middle and end of packing.

### 9.2. Number of samples, sampling quantity and testing

2 packs of 10's was taken at initial, middle and end from the packing belt. Tests were performed on composite sample: Description of pack, Sealing quality, Number of tablets in pack (count), Leak test (For 10's only).

## 10. Results and Discussion

Process validation of Prasugrel hydrochloride tablets Batch-1, Batch-2, and Batch-3 (Batch size: 10, 00, 000 tablets) had been carried out as per approved validation protocol and sampling plan. All the procedures carried out as

**Table 3:** Acceptance criteria for packing

(I) Description of pack	10 Tablets
(II) Cartons fill quantity	10 Blister
(III) Number of tablets in pack during packing	10 tablets
(IV) Sealing quality	Properly sealed
(V) Leak Test	No Blister shall fail

per specifications for blend, core tablet and coated tablet along with critical step of manufacturing such as milling, blending, lubrication, compression and packing.

## 11. Packing Process

After the inspection, the coated tablets were packed in the blisters on blister packing machine as per the BPR. The tablets were packed in 10's blister pack. The packing operation was monitored by sampling and testing the packs at initial, middle and end of packing operation. The results are summarized in below Table 5.

**Table 4:** Finished product analysis

Parameter	Specification	Bulk Tablets after Inspection					
		Observation		Batch-2		Batch-3	
		Batch-1					
Description	Yellowish beige color, oval shaped, film coated tablets with logo engraved on one side and plain on other side.	Complies		Complies		Complies	
Identification (by HPLC)	The retention time of major peak obtained in test solution should correspond to the chromatogram of the standard solution in the assay.	Complies		Complies		Complies	
Average weight	310.0 mg ± 2.0%	307.3 mg		304.3 mg		310.1 mg	
Thickness	4.4 mm ± 0.2 mm	4.6 mm		4.6 mm		4.6 mm	
Uniformity of dosage units	The acceptance value (AV) for 10 units should be NMT or equal to 15.0	8.1		9.7		2.9	
Disintegration Time	Not more than 30 minutes	6 min.34 sec		6 min. 59 sec		6 min.12 sec	
Weight built Up	Upto 2.9 to 3.0%	2.9		2.9		3.0	
Dissolution (by HPLC)	NLT 70.0% of the labeled amount of Prasugrel hydrochloride is dissolved in 30 min.	101.0%	100.1%	87.2%	94.5%	86.6%	94.9%
		100.7%	96.1%	76.9%	95.3%	71.0%	80.8%
		85.5%	91.1%	109.6%	92.4%	76.0%	83.2%
Assay (% Label Claim):Prasugrel hydrochloride ContentClaim:10 mg/tablet (5% overages)	NLT 97.0% and NMT 110.0% of the labeled amount of Prasugrel hydrochloride	98.9%		100.0%		99.9%	

**Table 5:** Packing process

Parameters	Specification	Batch-1	Batch-2	Batch-3
Description	For information	Complies	Complies	Complies
Sealing quality	Properly sealed	Complies	Complies	Complies
Count	10	10	10	10
Leak Test	Must be intact	Pass	Pass	Pass

## 12. Summary & Conclusion

On evaluation of results from three batches of “Prasugrel hydrochloride tablet 10 mg”, there was no significant variation between batch to batch and all the process variables were studied and therefore it can be concluded that the process of Prasugrel hydrochloride tablets for three batches stands validated. The results of all critical stage were found within the standard specification and acceptance criteria mentioned in the process validation protocol and finished product specification.

Hence manufacturing process of “Prasugrel hydrochloride tablet 10 mg” is considered validated and approved for routine production.

## 13. Source of Funding

None

## 14. Conflict of Interest

None

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