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Process Validation of Polmacoxib Capsule

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KEYWORDS

Process Validation, Polmacoxib , CPPs , CQAs , QA , cGMP

ABSTRACT: Process validation ensures consistency, quality, and compliance of the end product . This project is about process validation of capsule manufacturing, with an emphasis on optimizing and standardizing the production process to meet regulatory and quality requirements. The study includes the design, qualification, and validation of key manufacturing steps such as blending, granulation, encapsulation, and packaging. Critical parameters, such as uniformity of blend, weight variation, dissolution rate, and stability, are evaluated to establish reproducibility. The objective of this study is to optimize the manufacturing process of Polmacoxib while ensuring adherence to stringent quality assurance (QA) standards. This research explores critical process parameters (CPPs) and their impact on the critical quality attributes (CQAs) of Polmacoxib during its synthesis and formulation The results demonstrate that an optimized process ensures high yield, minimal impurities, and compliance with regulatory standards. The findings contribute to enhancing the scalability and reproducibility of Polmacoxib production, aligning with Good Manufacturing Practices (cGMP).

Objectives: To Assess and verify the Polmacoxib Capsule manufacturing process , long term product quality , consistency and regulatory compliance .

1. Introduction

Validation is establishing documented evidence which provide a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attribute. Process validation establishes the give and constraints in the manufacturing of process controls in an achievement of attractive attributes in the drug product while preventing undesirable properties. This important concept, since it serves to support the underlying definition of validation, which is a systematic approach to identification, measuring, evaluating, and documented, a series of significant steps in manufacturing process that require organize to ensure a reproducible of final product. Validation program depends upon information and understanding from product and manufacturing process development. This information and understanding are the basis of establishing an approach in control of manufacturing process that results in products with the desired quality.

Life Cycle of Validation:

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.

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Stages of process validation -

- Process Design .
- Process Qualification.
- Continued Process Verification

Types of Validation

- Prospective validation
- Concurrent Validation
- Retrospective Validation
- Revalidation

Prospective validation

It is characterized as the establishment of recorded proof that a system does what it supposes to do on the basis of a pre-planned protocol. This validation is typically conducted prior to the launch of new drugs and their manufacturing process. This approach to validation is usually followed whenever a new formula, procedure or facility must be tested prior to the start of routine pharmaceutical formulations.

a) Retrospective validation

It is characterized as the establishment of recorded evidence that the system does what it intends to do on the basis of a study and analysis of historical data. This is done by analysing historical data on production testing to demonstrate that the process has always been under control.

b) Concurrent validation

It is similar to prospective, except that the operating firm would sell the commodity to the public at its selling price during the certification period. This validation includes monitoring crucial processing steps and testing of the product. It is a replication of the validation process or a part of it. This shall be carried out when there is some adjustment or substitution in the formulation, equipment and position of the plant or site.

c) Revalidation

Periodic revalidations offers the opportunity to cross verify that the systems are still operating as originally validated and that no changes have affected the process system or piece of equipment's and the end results .

- Change in critical raw material (whether it is addition or deletion of another Raw material)
- Change or replacement of Equipment.
- Technology transfer or change in the facility.
- Change in Batch Size (Increase or decrease)

Major Phases in Validation

The activities relating to validation studies can be categorized in three parts:

Phase I- This is the pre-validation qualification phase, which includes all activities related to product research and development, development of pilot batch tests, scale-up testing, transfer of technology to commercial scale batches, establishing stability and storage conditions and handling of in-process and finished dosage forms, equipment qualification, master product.

Phase-II- This is the validation step of the process. It is intended to verify that all the defined limits of the critical process parameter are true and that satisfactory product can be generated even under the worst conditions.

Phase-III- Known as the Validation Maintenance step, It involves a regular review of all process relevant records, including the validation of audit reports, to ensure that no adjustments, irregularities, defects and improvements have been made to the production process and that all standard operating procedures and change control procedures have been followed. At this point, the validation team of individuals from all major departments also assures that there have been no changes or deviations that should have resulted in requalification and revalidation. Careful design and validation of systems and process controls will provide a high degree of trust that all lots or batches produced comply with their intended specifications. It is believed that during production and control, operations are carried out in compliance with the Good Manufacturing Practice concept, both in general and with a particular reference to sterile product manufacturing.

DRUG PROFILE

Drug name: Polmacoxib

Molecular formula: C18H16FNO4S.

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Molecular weight: 361.4 g/mol.

Chemical name: 4-(3-(3-fluorophenyl)-5, 5-dimethyl-4-oxo-4, 5-dihydrofuran-2-yl) benzene sulfonamide

Characters:

Description: Off white to yellowish color powder**.**

Solubility: Soluble in Acetonitrile & Dimethyl Sulphoxide

Moisture content: NMT 1.0 %

Loss on drying: NMT 1.0%

Residue on ignition: NMT 0.2%

Hydrogen Bond Donor Count: 01

Hydrogen Bond Acceptor Count: 06

Rotatable Bond Count: 03

Storage: Store in a tight light resistance & air resistance container at room temperature.

CATEGORY: Polmacoxib is a non-steroidal anti-inflammatory drug (NSAID) used for the treatment of osteoarthrosis and Degenerative Joint Disease (In this tissue of joint breakdown which causes stiffness , sealing near the joint and pain). It inhibits the enzymes carbonic anhydrase and COX-2.

DOSAGE & STRENGTH: Patient is advice to take 2 mg once in a day after a meal. The dose should not exceed 2 mg/day . If exceeds may lead to major side effects i.e. Liver damage .

2. Objective

- To Identify and evaluate Critical Process Parameter (CPPs)
- To assess Critical Quality Attributes (CQA's)of Polmacoxib capsule
- To investigate process optimization opportunities
- To ensure Consistency and Quality of Polmacoxib capsule
- To Contribute to the knowledge base on process validation

3. Methods

Sift Microcrystalline cellulose (PH-102) through 30#mesh & collect in suitable container with double line polythene bag. Take require quantity of Acetone (80% of total qty.) in past kettle/S.S. container. & Add Polmacoxib in it slowly under stirring to dissolve & make yellow color clear solution. (5 min). Load Microcrystalline Cellulose (PH-102) in RMG for 05 minutes impeller at slow speed chopper off . Add binder in rapid mixer granulator in slowly within 2 minutes under continuous mixing with impeller at slow speed chopper off. Extra Quantity of Acetone is add slowly within 2 minutes under continuous mixing with impeller at slow speed chopper off. Again after Kneading mixing for 3 minutes with impeller at slow speed and chopper off .(Extra quantity & time for kneading based on physical observation during granulation recommended granulation time is 7 minutes.) Discharge the wet mass in FBD bowl . Dry the wet mass in FBD bowl with inlet temperature 45ºC, till desired LOD with inter mediate raking. Check the LOD at 105ºC. With equipment moisture analyzer balance. Limit LOD (2.0 to 4.0 % w/w) Sift the dried granules with vibro sifter using 30#mesh sifter sieve. And mill the retained granules through multi-mill using 1.0 mm multi-mill screen at slow speed forward oriented & collect the sifted & mill granules in double lined polythene bag in HDPE container . Sift Magnesium Stearate with vibro sifter using 60#mesh sifter sieve & collect it in double lined polythene bag . Sift the Purified talc through 60#mesh sifter sieve & collect in suitable container with double line polythene bag. Sift the Colloidal silicon Dioxide through 40#mesh sifter sieve & collect in suitable container with double line polythene bag Load the dried granules & sifted following materials in octagonal blender and mix for 05 minutes at 13 rpm Add sifted following materials in octagonal blender and mix for 10 minutes at 13 rpm . Add Purified talc . Add sifted Magnesium stearate in octagonal blender and mix for 05 minutes at 13 rpm . Intimate QA person to take sample from blender & send QC department for bulk analysis

SETTING PARAMETERS

Table.1 Setting Parameter for Capsule filling

S .no	PARAMETERS	LIMITS
1.	Appearance	Size "4" hard gelatin capsules pink cap & transparent body filled with off white to Creamish granular powder.

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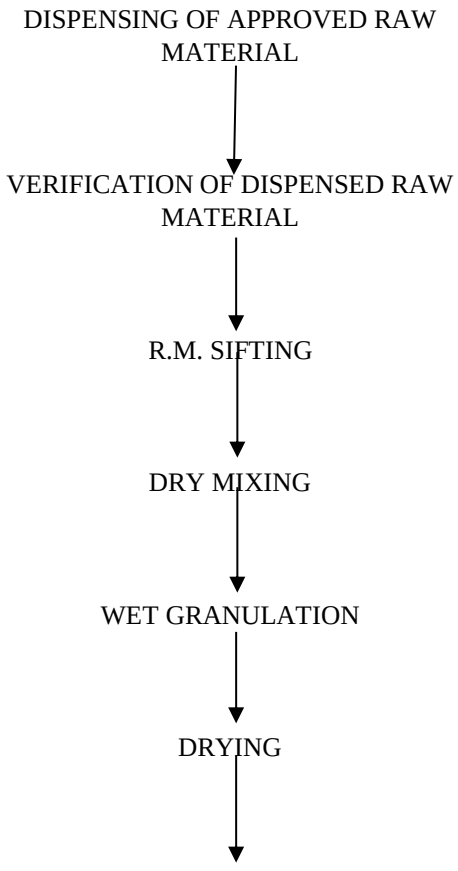
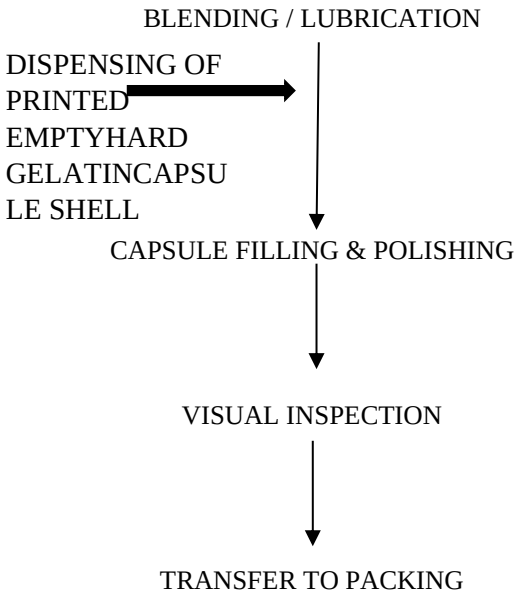
2.	Average wt. of filled capsule	135 mg±10%(121.50 mg to 148.5 mg)
3.	Average net filled weight each capsule	95 mg ±10% (85.5 mg to 104.5mg)
4.	Theoretical fill wt. of 20 capsules	2.7 g ±3% (2.619 g to 2.781 g)
5.	Uniformity of fill weight	NMT two of the individual mass content deviate from the average net mass by NMT ± 10 % & none deviate by more than 20 %.
6.	Locking Length	14.30 mm±0.7 mm.(13.60 mm to 15.00mm)
7.	Disintegration Time	NMT 30 minutes.

FLOW DIAGRAM:





4. Results

4.1 Records of Results from Dispensing activity to Blending of the Granules

Table.2 Records of Results from Dispensing activity & sifting

Sr. No.	Test Parameter	Limit	Acceptance Criteria	Results		
				Batch number PC01	Batch number PC02	Batch number PC03
1.	Dispensing (API)	Temperature (°C)	Should not exceeds 25°C	18.2 °C	19.7 °C	18.2 °C
		Relative Humidity (%)	Should not exceeds 55%	42%	53%	42%
2.	Sifting	Shall be passed from the	#30	Complies	Complies	Complies

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Sr. No.	Test Parameter	Limit	Acceptance Criteria	Results		
				Batch number PC01	Batch number PC02	Batch number PC03
		mesh and there shall not be retains over the sifter sieve				

4.2 Record of Results of Drying (LOD) activity

Table.3 Records of Results of Drying

Sr. No	Test parameter	Specification limit	Results		
			Batch number PC01	Batch number PC02	Batch number PC03
1.0	**Description**	White or Off white creamish coloured granular powder	Complies	Complies	Complies
2.0	**LOD**	Between 2.0% to 4.0 % w/w	3.20	3.01	2.36
3.0	**Residual solvent**	Acetone : Not more than 5000ppm	Not detected	Not detected	Not detected

4.3 Analytical results of Lubricated Blend

Sampling done from different locations to analyse the Blend Uniformity , Related Substance test and Assay of lubricated blend and found well within the predefine Specification limit

Table.4 Setting parameters for Lubricated Blend

S .no	PARAMETERS	LIMITS
1.	Blend Uniformity	95.0 % to 105.0 %
2.	Related Substance test (By HPLC)	
	Any individual unknown impurity	NMT 0.5%
	Total impurities	Not more than 1.5%
3.	Assay	Between 90.0% to 110 %

4.4 Record of Results of capsule filling Activity

Sampling done at different speeds of filling (i.e. Maximum speed ,Optimum speed ,Minimum speed and Composite) to analyze the Description , Identification , Average weight of fill capsules , Average net fill weight , Uniformity of filled weight , Dissolution , Disintegration time ,Content Uniformity , Related substance & Assay of filled capsule and found the results well within the predefine Specification limit

Table.5 Setting parameters for Lubricated Blend

S .no	PARAMETERS	LIMITS
1.	Description	Size “4” Hard gelatin capsules with pink caps & transparent body filled with off white to Creamish granular powder
2.	Identification (By HPLC)	The retention time of major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard preparation as obtained in the assay

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3.	Average weight of filled capsules	135mg ±10.0 %
4.	Average net fill weight	95mg ±10.0 %
5.	Uniformity of Filled Weight	Not more than two of the individual mass contents deviate from the average net mass by more than ± 10% and none deviates by more than ± 20%
6.	Disintegration time	NMT 30.0 Minutes
7.	Dissolution	NLT 75% (Q) in 45 minutes
8.	Related substance	
	Any individual unknown impurity	Not more than 0.5%
	Total impurities	Not more than 1.5%
9.	Content uniformity	Limit (L1) should be less than or equal to 15.0 Limit (L2) should be less than or equal to 25.0
10.	Assay (By HPLC)	Between 90.0% to 110.0 %

4.5 Record of Results of Packaging Activity

Table.6 Record of results of Packing Activity

S. No.	Test Parameter	Acceptance Criteria	Results		
			Batch number PC01	Batch number PC02	Batch number PC03
1.	Sealing Temperature	180^0C – 200 ^{0}C	198^0C	197^0C	198^0C
	Formation of Base foil	Should be uniform	OK	OK	OK
	Knurling	Should be uniform	OK	OK	OK
	Cutting	Should be sharp and readable	OK	OK	OK
	Batch Embossing / coding	Should be uniform	OK	OK	OK
	NFD Camera challenge	Should be uniform	OK	OK	OK
	Leak Test	Should be pass	Pass	Pass	Pass

4.6 Finished Product Analytical Result

- **For first process Validation batch**

Table.7 Record of results of Finish Products

S.No.	**Test Parameter**	**Acceptance Criteria**	**Results**
			Batch number PC01
1.0	**Description**	Size “4” Hard gelatin capsule with pink cap and transparent body filled with off white to creamish granular powder	Size “4” Hard gelatin capsule with pink cap and transparent body filled with off white to creamish granular powder
2.0	**Identification**		

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S.No.	Test Parameter	Acceptance Criteria	Results Batch number PC01
	By HPLC	The retention time of major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard preparation as obtained in the assay .	The retention time of major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard preparation as obtained in the assay .
3.0	**Average Weight of filled capsules**	135.0 ± 10%	134.93mg
4.0	**Average Net Filled Weight**	95.00± 10%	94.48 mg
5.0	**Uniformity of Filled Weight**	Not more than two of the individual mass contents deviate from the average net mass by more than ± 10% and none deviates by more than ± 20%	(-) 3.04 % to (+) 6.72 %
6.0	**Disintegration time**	Not more than 30 minutes	03 min 43 sec
7.0	**Dissolution:**	NLT 75% (Q)of the labeled amount of Polmacoxib should dissolve in 45 minutes	95.01 % to 99.90 %
8.0	**Related Substances Test (By HPLC)**		
	Any individual unknown impurity	Not more than 0.5%	0.085 %
	Total impurities	Not more than 1.5%	0.615 %
9.0	**Residual Solvent**		
	Acetone	Not more than 5000ppm	Not detected
10.0	**Content uniformity**	Acceptance value of the first 10 dosage units is less than or equal to L1% . If the acceptance value is >L1 % ,Test the next 20 units . Final acceptance value of the 30 dosage units is ≤L1% ,and no individual content of any dosage unit is less than [1-(0.01)(L2)]M nor more than [1+(0.01)(L2)] M L1=15.0 & L2=25.0	4.13

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S.No.	Test Parameter	Acceptance Criteria	Results Batch number PC01
11.	**Assay (By HPLC)**	Between 90.0% to 110.0 %	99.9%
12.0	**Microbial limit test**		
	Total Aerobic Microbial count	NMT 1000 cfu/gm	20cfu/g
	Total Yeast & Mold count	NMT 100 cfu/gm	<10 cfu/g
	E.Coli	Should be Absent in 1 gm	Absent in 1 gm

- **For second process Validation batch**

Table.8 Record of results of Finish Products

S.No.	Test Parameter	Acceptance Criteria	Results Batch number PC02
1.0	**Description**	Size "4" Hard gelatin capsule with pink cap and transparent body filled with off white to creamish granular powder	Size "4" Hard gelatin capsule with pink cap and transparent body filled with off white to creamish granular powder
2.0	**Identification**		
	By HPLC	The retention time of major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard preparation as obtained in the assay .	The retention time of major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard preparation as obtained in the assay .
3.0	**Average Weight of filled capsules**	135.0 ± 10%	135.96 mg
4.0	**Average Net Filled Weight**	95.00± 10%	96.05mg
5.0	**Uniformity of Filled Weight**	Not more than two of the individual mass contents deviate from the average net mass by more than ± 10% and none deviates by more than ± 20%	(-) 4.60 % to (+) 4.26 %
6.0	**Disintegration time**	Not more than 30 minutes	05 min 09 sec
7.0	**Dissolution:**	NLT 75% (Q)of the labeled amount of Polmacoxib should dissolve in 45 minutes	91.26 % to 96.75 %

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S.No.	Test Parameter	Acceptance Criteria	Results Batch number PC02
8.0	**Related Substances Test (By HPLC)**		
	Any individual unknown impurity	Not more than 0.5%	0.190 %
	Total impurities	Not more than 1.5%	0.514 %
9.0	**Residual Solvent**		
	Acetone	Not more than 5000ppm	Not detected
10.0	**Content uniformity**	Acceptance value of the first 10 dosage units is less than or equal to L1% . If the acceptance value is >L1 % ,Test the next 20 units . Final acceptance value of the 30 dosage units is ≤L1% ,and no individual content of any dosage unit is less than [1-(0.01)(L2)]M nor more than [1+(0.01)(L2)] M L1=15.0 & L2=25.0	0.64
11.	**Assay (By HPLC)**	Between 90.0% to 110.0 %	102.7%

S.No.	Test Parameter	Acceptance Criteria	Results Batch number PC02
12.0	**Microbial limit test**		
	Total Aerobic Microbial count	NMT 1000 cfu/gm	20 cfu/g
	Total Yeast & Mold count	NMT 100 cfu/gm	<10 cfu/g
	E.Coli	Should be Absent in 1 gm	Absent in 1 gm

- **For Third process Validation batch**

Table.9 Record of results of Finish Products

S.No.	Test Parameter	Acceptance Criteria	Results Batch number PC03
1.0	**Description**	Size “4” Hard gelatin capsule with pink cap and transparent body filled with off white to creamish granular powder	Size “4” Hard gelatin capsule with pink cap and transparent body filled with off white to creamish granular powder
2.0	**Identification**		
	By HPLC	The retention time of major peak in the chromatogram of the test solution corresponds to that in the	The retention time of major peak in the chromatogram of the test solution corresponds

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S.No.	Test Parameter	Acceptance Criteria	Results Batch number PC03
		chromatogram of the standard preparation as obtained in the assay .	to that in the chromatogram of the standard preparation as obtained in the assay .
3.0	**Average Weight of filled capsules**	135.0 ± 10%	136.89 mg
4.0	**Average Net Filled Weight**	95.00± 10%	97.22mg
5.0	**Uniformity of Filled Weight**	Not more than two of the individual mass contents deviate from the average net mass by more than ± 10% and none deviates by more than ± 20%	(-) 5.21 % to (+) 5.82 %
6.0	**Disintegration time**	Not more than 30 minutes	07 min 25 sec
7.0	**Dissolution:**	NLT 75% (Q)of the labeled amount of Polmacoxib should dissolve in 45 minutes	100.11 % to 101.81 %
8.0	**Related Substances Test (By HPLC)**		
	Any individual unknown	Not more than 0.5%	0.188%
	impurity		
	Total impurities	Not more than 1.5%	0.682%
9.0	**Residual Solvent**		
	Acetone	Not more than 5000ppm	Not detected
10.0	**Content uniformity**	Acceptance value of the first 10 dosage units is less than or equal to L1% . If the acceptance value is >L1 % ,Test the next 20 units . Final acceptance value of the 30 dosage units is ≤L1% ,and no individual content of any dosage unit is less than [1-(0.01)(L2)]M nor more than [1+(0.01)(L2)] M L1=15.0 & L2=25.0	7.12
11.	**Assay (By HPLC)**	Between 90.0% to 110.0 %	102.20%
12.0	**Microbial limit test**		
	Total Aerobic	NMT 1000 cfu/gm	15 cfu/g

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S.No.	Test Parameter	Acceptance Criteria	Results
			Batch number PC03
	Microbial count		
	Total Yeast & Mold count	NMT 100 cfu/gm	<10 cfu/g
	E.Coli	Should be Absent in 1 gm	Absent in 1 gm

5. Discussion

All the process variables were monitored for manufacturing process of product Polmacoxib capsule at different stages of manufacturing as defined in sampling plan of approved Process validation Protocol .The manufacturing process was executed as per approved batch manufacturing and batch packing record. The process variables were monitored at the granulation stage for process validation batch i.e., B. No. PC01, PC02 & PC03. The sample was withdrawn at Lubrication stage, Filling stage and packing stage as per approved process validation protocol. All the analytical results were found well meets the Acceptance Criteria limit .This validation report proves that the manufacturing process of Polmacoxib Capsule procedure works in consistent manner and reliable to product high quality end products and medicines which are safe and efficient for patient use .

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