WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Process Validation of Optimized Formulation of Levocetirizine Dihydrochloride (Lev) Tablet Dosage Form

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ABSTRACT

Process validation helps to maintain the quality of the drug products manufactured and monitoring the drug quality at each critical stage of manufacturing. There are many steps in the manufacturing process of tablet dosage form which includes mixing, granulation, drying, compression and packaging. The quality of the drug is to be maintained at each and every step of the manufacturing process and it is ensured by process validation. Quality is to build in while manufacturing of the dosage form, end product testing is not enough, and therefore process validation is the way to confirm that the manufacturing process is validated and produces dosage form meeting its acceptance criteria. Process validation is an essential necessity in any pharmaceutical industry. After search report summary of patent it is concluded that for Levocetirizine tablet, There is no any process validation documents are available.

KEYWORDS: Process validation, optimization, comprehensible, levocetirizine, Master plan

INTRODUCTION

Validation is accessible and comprehensible to others involved in each stage of the lifecycle. Information transparency and accessibility are fundamental tenets of the scientific method. They are also essential to enabling organizational units responsible and accountable for the process to make informed, science-based decisions that ultimately support the release of a product to commerce.

- Validation Master Plan
- Validation Protocol
- Validation Report
- SOPs

Validation Master Plan:

An approved written plan of objectives and actions stating how and when a company will achieve compliance with the GMP requirements regarding validation. VMP is a summary intention document stating the scope of the validation and outlining the methods to be used to establish the performance adequacy. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of its being the list/ inventory of the items to, relevant to

Validation Protocol:

- Protocol Approval Sheet
- Table of content
- Objective and Scope
- Validation team and responsibility
- Steps for validation and acceptance criteria
- Process validation plan

- Evaluation of active raw material
- Evaluation of formulation ingredients
- Evaluation of equipment
- Responsibility
- Manufacturing process flow chart
- Product details

Validation Report:

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated). The report should include at least the following:

- Title and objective of study
- Reference to protocol
- Details of material
- Equipment
- Programmes and cycles used
- Details of procedures and test methods
- Results (compared with acceptance criteria)
- Recommendations on the limit and criteria to be applied on future basis.

SOP (Standard Operating Procedure):

- Standard Operating Procedures (SOPs) are issued to specifically instruct employees in areas of responsibility, work instructions, appropriate specifications and required records.
- These outline procedures, must be followed to claim compliance with GMP principles or other statutory rules and regulations.
- The general aspects covered under the SOPs are the Preparation and maintenance of work area like washing and sterilization, decontamination and testing area. Even the work done in the laboratory were documented, for example, the laboratory operations involving the receipt of reagents, standards, preparation of reagents, labelling and storage, test procedures, reference material, identification, handling, storage and use deviations, errors. Even the details of the equipment and their maintenance were also involved.

MATERIAL AND METHOD:

Table No. 1 Lists of Materials

S. No.	Material
1	Levocetirizine IH
2	Cellulose microcrystalline (AVICEL PH112) EP
3	Lactose anhydrous (Supertab 21AN) BP/Ph.Eur.
4	Sodium starch Glycollate (Glycolys LV) EP
5	Magnesium Stearate BP

Table No. 2 List of Methods

S. No.	Methods
1	Loss on Drying
2	Weight Variation
3	hardness
4	Thickness
5	Friability testing
6	Disintegration time

RESULTS:

Table No. 3

Sr. No.	Stage and Parameters	Acceptance criteria in MMD-I	Recommendations for commercial validation batch manufacturing
1	Knives direction of Multi mill	Forward direction	Forward direction
2	Milling speed of Multi mill	Medium speed	Medium speed
PRE-LUBRICATION :			
3	Mixing time	3 minutes	3 minutes
4	Mixing Speed	12 RPM	12 RPM
5	Granulation yield	95 % to 100 %	98 % to 100 %
COMPRESSION (45 STATION DOUBLE ROTARY COMPRESSION MACHINE):			
6	Turret Speed (T)	To be recorded	10 to 40 RPM (Optimum: 21 to 29 RPM)
7	Feeder Speed (F)	To be recorded	4 to 10 RPM
8	Thickness	3.25 mm ± 0.30 mm (2.95 mm to 3.55 mm)	3.25 mm ± 0.30 mm (2.95 mm to 3.55 mm)
9	Hardness	6.00 ± 3.00 kg/cm^2 (3.00 to 9.00 kg/cm^2) OR (30 N to 90 N)	6.00 ± 3.00 kg/cm^2 (3.00 to 9.00 kg/cm^2) OR (30 N to 90 N)
10	Compression yield	97 % to 100 %	97 % to 100 %
11	Batch yield	95 % to 100 %	95 % to 100 %
12	Inspection yield	95 % to 100 %	95 % to 100 %
13	Batch yield	93 % to 100 %	93 % to 100 %

DISCUSSION:

- Levocetirizine Dihydrochloride (Lev) TABLETS 50 mg, Batch No. 1, 2 and 3 were taken as per approved process validation protocol.
- Active pharmaceutical ingredient, Levocetirizine IH used for manufacturing of three validation batches were procured from “LEE PHARMA LIMITED” approved vendor only.
- Manufacturing of three validation batches were performed as per instructions mentioned in MMD-I & all samples were withdrawn during manufacturing as per approved protocol PV and sample were submitted to QC for analysis.

A) Granulation: - During the Granulation process all the critical process parameters like inlet temperature, products temperature, peristaltic pump speed, exhaust temperature, atomization air pressure, spray rate, Exhaust flap, Total drying time & Loss on drying were reviewed and observed adequate to achieve desired quality of granules.

B) Lubrication: Lubrication process was carried out as per MMD-I and results of composite sample were reviewed and found within the acceptance criteria. Uniformity of blend results for Levocetirizine was reviewed and found within the acceptance criteria.

C) Compression Stage:

a. Manufacturing of validation batches was performed as per instructions mentioned in the MMD-I.

b. Compression was carried out on 45 station double rotary compression machine using with specified setting parameters and the punches and dies as mentioned in the MMD-I.

I. Compression machine speed challenge study:

c. The ruggedness of compression machine was challenged by machine at slow speed (10 RPM), optimum speed (20 RPM) and high speed (30 RPM) for Batch No.: 1 and 2.

d. The ruggedness of compression machine was challenged by machine at slow speed (10 RPM), optimum speed (25 RPM) and high speed (40 RPM) for Batch No.: 3.

e. All the physical parameters were reviewed at slow, optimum and high speed of compression machine and found within the acceptance criteria.

f. The variation in the speed within the specified range does not affect the quality parameters of the product.

g. Results of uniformity of dosage units (by content uniformity) for slow and high speed for all three batches were reviewed and found within he acceptance criteria.

II. Tablets hardness challenge study:

a. Study was performed at low hardness (28 N to 40 N), Optimum hardness (51 N to 69 N), and high hardness (76 N to 89 N) of the tablets for Batch No. 1

b. Study was performed at low hardness (31 N to 49 N), Optimum hardness (40 N to 56 N), and high hardness (72 N to 88 N) of the tablets for Batch No. 2

c. Study was performed at low hardness (28 N to 39 N), Optimum hardness (49 N to 72 N), and high hardness (75 N to 92 N) of the tablets for Batch No. 3

d. All the physical parameters were reviewed at low hardness, optimum hardness and high hardness of compressed tablets and found within the acceptance criteria except hardness at low and high hardness. Hardness may goes out of limit as this is challenge study for hardness.

e. Dissolution study was performed at Low hardness and high hardness were reviewed and found within the acceptance criteria.

III. First and last round of tablets during compression:

a. Study was performed at first and last round of tablets during compression at optimum speed and optimum hardness.

b. All the physical parameters were reviewed at first and last round of tablets during compression and found within acceptance criteria.

IV. Critical quality attributes at different stages of compression:

a. The performance of the machine (compression process) to produce consistence product was evaluated by inspection of sample coveringinitial, middle & end stage of compression were reviewed and found within acceptance criteria.

b. Results of uniformity of dosage units (by content uniformity) at different stages of compression i.e. initial, middle and end stage of compression at optimum speed and optimum hardness were reviewed and found within the acceptance criteria.

c. Yield at different stages were reviewed and found within the acceptance criteria.

d. No Deviation and out of specification (OOS) were observed during manufacturing of validation batches and during the QC analysis.

e. All the finished product results were compiled the specifications of finished product.

f. From the process validation study, it is concluded that a manufacturing process used for manufacturing of LEVOCETIRIZINE TABLETS 50 mg stands validated, have acceptable level of output variability for desired CQA and the applied control strategy is in line with required CPP and is released for commercial manufacturing including all the recommendations.

g. Following recommendations are observed during manufacturing of validation batches based on these MMD-I shall be revised.

CONCLUSION:

- Levocetirizine Dihydrochloride (Lev) TABLETS 5 mg, were taken as per approved process validation protocol.
- Active pharmaceutical ingredient, Levocetirizine IH used for manufacturing of three validation batches were procured from “LEE PHARMA LIMITED” approved vendor only.

CONFLICTS OF INTEREST:

No conflicts of interest.

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