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Research Article

Process Validation of Sevelamer Hydrochloride Film Coated Tablet

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Abstract

All the three batches resulted in granules with desired flow and compaction which is evident from the data of compressed tablets. At compression stage Weight parameters and Speed parameters evaluated and found within Specified limit as well as, The Statistical analysis process performance is high capable, Data is normal and Z bench value also give assurance that process remains in state of control (Process validation state) during manufacturing of Sevelamer Hydrochloride film coated tablets, 800 mg. Coating process proven as validated from the weight build up data of tablets as validation data provided for after 50% coating, 75% coating and 100% coating and found in accordance with process validation protocol. Finished product result was evidence of Weight gain while the inspection activity as this material is in very high hygroscopic in nature. However results found within specified limit.

Keywords: Z bench value, Sevelamer Hydrochloride, Process validation, cGMP.

INTRODUCTION:

Validation is a tool of quality assurance which provides confirmation of the quality in equipment system, manufacturing process, software and testing methods. Validation of the individual step of manufacturing processes is called the process validation. The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid-1970s in order to improve the quality of pharmaceuticals. Assurance of product quality is derived from careful attention to number of factors including selection of quality parts and materials, adequate product and process design, control of the process, and in process and end product testing.¹

Process Validation has now become a part of Current Good

Manufacturing Practices Regulations (cGMP), it is mandatory for manufacturer to go through Process Validation much more rigorously than earlier.²

Types of Validation

- Process validation
- Equipment validation
- Utility validation
- Cleaning validation
- Analytical method validation
- Vendor validation

Drug Profile:

Sr.No	Parameter	SEVELAMER HYDROCHLORIDE
1.	Structure	
2.	IUPAC name	2-(chloromethyl)oxirane prop-2-en-1-amine hydrochloride
3.	Category	Phosphate binding agent
4.	Molecular formula	C ₆ H ₁₂ Cl ₂ NO
5.	Molecular weight	186.08 g/mol
6.	CAS registry number	152751-57-0
7.	Solubility	Insoluble in water
8.	pKa value	-4.2
9.	Melting Point	298 °C to 304 °C
10.	CDSCO Approval	10-07-2007
11.	Storage	Store at controlled room temperature 15°C to 30°C. Protect from moisture.
12.	Use	Hyperphosphatemia, Renal dialysis
13.	Mechanism of action	Sevelamer is a non-absorbable polymeric amine and phosphate binding agent which is used to prevent hyperphosphatemia. Upon oral administration, the amine groups in sevelamer become protonated in the intestines and bind to the dietary phosphate groups in the gastrointestinal tract, through preventing the absorption of phosphate and controlling the phosphate plasma level.

Purpose of Validation:

The purpose of this validation study is establishing documented evidence that the specified manufacturing process employed to manufacture Sevelamer Hydrochloride film coated tablets, 800 mg is capable of producing the product meeting all its predetermined specifications and quality attributes consistently and reproducibly. Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory and exhibit batches. Information and data should demonstrate that the manufacturing process is capable of consistently producing acceptable quality products within manufacturing conditions. A successful validation program depends upon information and knowledge from product and preset the development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process those results in products with the desired quality attributes.

Responsibility:**Quality Assurance:**

➤ The QA personnel are responsible for the preparation of the protocol, conducting the sampling at designated stages and its documentation. The QA personnel are also responsible to compile the results and prepare a Process Validation report and summary.

➤ The QA Head is responsible to review this protocol, Process validation report and summary for its completeness and correctness.

Production:

➤ Production is responsible to follow the protocol and adhere to the requirements of the protocol. Production shall be responsible to provide necessary support to QA to conduct this validation study. Production is also responsible to intimate QA for sampling at respective stages and shall provide necessary resources.

➤ The Production Head is responsible to review the protocol, Process validation report and summary for its completeness and correctness.

Quality Control:

➤ Quality Control is responsible to review the requirements of the protocol and to analyze the samples sent by QA in accordance to the protocol and report the results. The microbiologist is responsible for carrying out the

environmental monitoring of the area as per attached plan and location diagram. The environment monitoring report shall be prepared by the Head Microbiology.

- The QC Head is responsible to review the protocol, Process validation report and summary for its completeness and correctness.

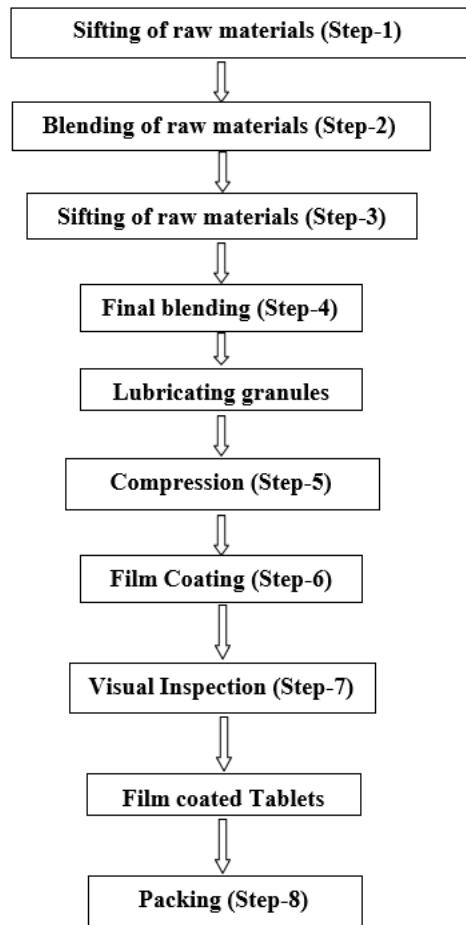
Engineering:

- Engineering is responsible to review the requirements of the protocol and to Install, qualify and certify plant, facilities, equipment, and supportive systems.

List of Equipments/Instruments:

S. N.	EQUIPMENT/ INSTRUMENTS NAME
01	Weighing balance (Dispensing - 100 kg, 10 Kg & 300 mg)
02	Weighing balance (Granulation area - 200 kg)
03	Vibrorotatory Sifter (20#, 30# and 60#)
04	Octagonal blender (300 L)
05	Compression Machine 15 Station D tooling Machine
06	De-duster
07	Metal detector
08	Weighing balance (Compression Quarantine - 200 kg)
09	Weighing balance (IPQC - 220 mg)
10	Vernier caliper
11	Hardness tester
12	Friabilator
13	Disintegration Apparatus
14	Solution Preparation tank
15	Solution tank with stirrer
16	Auto coater 48" (125 Kg)
17	Weighing balance (Coating Quarantine - 200 kg)
18	Inspection table
19	Weighing balance (Inspection Quarantine - 200 kg)

PROCESS FLOW CHART



Process Flow Diagram: Process Flow Diagram

EQUIPMENTS/ INSTRUMENTS	PROCESS	CHECKS
Weighing balance (100 kg, 10 Kg & 300 mg)	Dispensing of Raw materials <ul style="list-style-type: none"> • Dispersed all raw materials as per RMR and approved BMR. 	<ul style="list-style-type: none"> • Ensure Area cleanliness before starting the activity. • Ensure cleanliness of containers, Weighing balance and RLAF. • Ensure Temperature, % RH and differential pressure of area is within limit. • Ensure calibration, verification & preventive maintenance status of weighing balance before Operation. • Ensure validation of RLAF. • Ensure differential pressure of RLAF is within limit.
Weighing balance (200 kg)	Verification of dispensed Material <ul style="list-style-type: none"> • Verify All dispensed raw materials against RMR and approved BMR. 	<ul style="list-style-type: none"> • Ensure Area cleanliness before starting the activity. • Ensure cleanliness of containers and Weighing balance. • Ensure Temperature, % RH and Differential pressure of area is within limit. • Ensure calibration, verification & preventive maintenance status of weighing balance before Operation.
Vibratory Sifter 30#, 20#	Sifting of raw materials <ul style="list-style-type: none"> • Sift the raw materials - Sevelamr 	<ul style="list-style-type: none"> • Ensure Temperature, % RH and Differential pressure of area is within limit.

	Hydrochloride, Microcrystalline Cellulose and Croscarmellose sodium through 30# and Colloidal silicon dioxide through 20# of Vibratory Sifter.	<ul style="list-style-type: none"> Ensure Qualification & preventive maintenance status of Vibratory Sifter before Operation. Sieve integrity.
Octagonal Blender (300 L)	Blending of sifted raw materials <ul style="list-style-type: none"> Mix the above sifted raw materials in Octagonal blender for 30 minutes at 8RPM. 	<ul style="list-style-type: none"> Ensure Temperature, % RH and Differential pressure of area is within limit. Ensure Qualification, calibration & preventive maintenance status of Octagonal Blender before Operation.
Vibratory Sifter 60#	Sifting of lubrication material <ul style="list-style-type: none"> Sift the lubrication material through 60# of Vibratory Sifter. 	<ul style="list-style-type: none"> Ensure Temperature, % RH and Differential pressure of area is within limit. Sieve integrity.

EQUIPMENTS/ INSTRUMENTS	PROCESS	CHECKS
Octagonal Blender (300 L), Containers and Weighing balance(200 kg)	Blending of lubrication material <ul style="list-style-type: none"> Add sifted lubrication material in Octagonal blender and mix for 08 minutes at 8 RPM and Send sample to QC for analysis. If blend uniformity not achieved then mix for 01 minutes at 8 RPM and Send sample to QC for analysis. If again blend uniformity not achieved then mix for 01 minutes at 8 RPM Send sample to QC for analysis and unload the material in Containers and weigh the material and transfer the material with proper labeling in compression quarantine area. 	<ul style="list-style-type: none"> Ensure Temperature, % RH and Differential pressure of area is within limit. Ensure cleanliness of containers.
Compression machine 15 station, Containers, Weighing balance(200 Kg), Weighing balance(220 mg), Vernier caliper, Hardness tester, Friabilator, Disintegration Apparatus, De-duster and metal detector	Tablet Compression <ul style="list-style-type: none"> Compress the tablets from QC Approved bulk and simultaneously pass the tablets through de-duster and metal detector. Collect the good tablets in containers and weigh it and transfer the compressed tablets with proper labeling in compression quarantine area. 	<ul style="list-style-type: none"> Ensure Area cleanliness before starting the activity. Ensure Temperature, % RH and differential pressure of area is within limit. Ensure cleanliness of containers, Equipments and Instruments. Ensure Qualification, calibration & preventive maintenance status of Equipments and Instruments. In-process tests as required frequency. To be sampled as mentioned in sampling plan.
Solution preparation tank, solution tank with stirrer, Autocoater 48" (125 Kg), weighing balance 200 Kg and containers.	Tablet Coating <ul style="list-style-type: none"> Prepare the coating solution - take purified water in Solution preparation tank and add Opadry AMB II clear 88A190022 under continuous stirring and stir it for 60 minutes. Filter the solution through 100# filter cloth and transfer the coating solution in solution tank with stirrer. Coat the QC approved compressed tablets from QC Approved tablets, weigh it and transfer the coated tablets with proper labeling in coating quarantine area. 	<ul style="list-style-type: none"> Ensure Area cleanliness before starting the activity. Ensure Temperature, % RH and differential pressure of area is within limit. Ensure cleanliness of containers, Equipments and Instruments. Ensure Qualification, calibration & preventive maintenance status of Equipments and Instruments. To be sampled as mentioned in sampling plan.

EQUIPMENTS/INSTRUMENTS	PROCESS	CHECKS
Weighing balance(100 kg, 10 Kg & 300 mg)	<p><u>Dispensing of Raw materials</u></p> <ul style="list-style-type: none"> • Dispersed all raw materials as per RMR and approvedBMR. 	<ul style="list-style-type: none"> • Ensure Area cleanliness before starting the activity. • Ensure cleanliness of containers, Weighing balance and RLAF. • Ensure Temperature, % RH and differential pressure of area is within limit. • Ensure calibration, verification & preventive maintainace status of weighing balance before Operation. • Ensure validation of RLAF. • Ensure differential pressure of RLAF is within limit.
Weighing balance(200 kg)	<p><u>Verification of dispensedMaterial</u></p> <ul style="list-style-type: none"> • Verify All dispensed raw materials against RMR and approved BMR. 	<ul style="list-style-type: none"> • Ensure Area cleanliness before starting the activity. • Ensure cleanliness of containers and Weighing balance. • Ensure Temperature, % RH and Differential pressure of area is within limit. • Ensure calibration, verification & preventive maintainace status of weighing balance before Operation.
Vibratory Sifter30#, 20#	<p><u>Sifting of raw materials</u></p> <ul style="list-style-type: none"> • Sift the raw materials - Sevelamr Hydrochloride, Microcrystalline Cellulose and Croscarmellose sodium through 30# and Colloidal silicon dioxide through 20# of Vibratory Sifter. 	<ul style="list-style-type: none"> • Ensure Temperature, % RH and Differential pressure of area is within limit. • Ensure Qualification & preventive maintainance status of Vibratory Sifter before Operation. • Sieve integrity.
OctagonalBlender (300 L)	<p><u>Blending of sifted raw materials</u></p> <ul style="list-style-type: none"> • Mix the above sifted raw materials in Octagonal blender for 30 minutes at 8RPM. 	<ul style="list-style-type: none"> • Ensure Temperature, % RH and Differential pressure of area is within limit. • Ensure Qualification, calibration & preventive maintainance status of Octagonal Blender before Operation.
Vibratory Sifter60#	<p><u>Sifting of lubrication material</u></p> <ul style="list-style-type: none"> • Sift the lubrication materialthrough 60# of Vibratory Sifter. 	<ul style="list-style-type: none"> • Ensure Temperature, % RH and Differential pressure of area is within limit. • Sieve integrity.

EQUIPMENTS/INSRUMTENTS	PROCESS	CHECKS
Octagonal Blender (300 L), Containers and Weighing balance(200 kg)	<p><u>Blending of lubrication material</u></p> <ul style="list-style-type: none"> • Add sifted lubrication material in Octagonal blender and mix for 08 minutesat 8 RPM and Send sample to QC for analysis. • If blend uniformity not achieved then mix for 01 minutes at 8 RPM and Send sample to QC for analysis. • If again blend uniformity not achieved then mix for 01 minutes at 8 RPM Send sample to QC for analysis and unload the material in Containers and weigh the material and transfer the material with proper labeling in compression quarantine area. 	<ul style="list-style-type: none"> • Ensure Temperature, % RHand Differential pressure ofarea is within limit. • Ensure cleanliness ofcontainers.
Compression machine 15 station, Containers, Weighing balance(200	<p><u>Tablet Compression</u></p> <ul style="list-style-type: none"> • Compress the tablets from QC Approved bulk and and simultaneously pass the tablets through de-duster and 	<ul style="list-style-type: none"> • Ensure Area cleanliness before starting the activity. • Ensure Temperature, % RH and

Kg), Weighing balance (220 mg), Vernier caliper, Hardness tester, Friabilator, Disintegration Apparatus, De- duster and metal detector	<p>metal detector.</p> <ul style="list-style-type: none"> Collect the good tablets in containers and weigh it and transfer the compressed tablets with proper labeling in compression quarantine area. 	<p>differential pressure of area is within limit.</p> <ul style="list-style-type: none"> Ensure cleanliness of containers, Equipments and Instruments. Ensure Qualification, calibration & preventive maintenance status of Equipments and Instruments. In-process tests as required frequency. To be sampled as mentioned in sampling plan.
Solution preparation tank, solution tank with stirrer, Autocoater 48" (125 Kg), weighing balance 200 Kg and containers.	<p>Tablet Coating</p> <ul style="list-style-type: none"> Prepare the coating solution - take purified water in Solution preparation tank and add Opadry AMB II clear 88A190022 under continuous stirring and stir it for 60 minutes. Filter the solution through 100# filter cloth and transfer the coating solution in solution tank with stirrer. Coat the QC approved compressed tablets from QC Approved tablets, weigh it and transfer the coated tablets with proper labeling in coating quarantine area. 	<ul style="list-style-type: none"> Ensure Area cleanliness before starting the activity. Ensure Temperature, % RH and differential pressure of area is within limit. Ensure cleanliness of containers, Equipments and Instruments. Ensure Qualification, calibration & preventive maintenance status of Equipments and Instruments. To be sampled as mentioned in sampling plan.

EQUIPMENTS/INSTRUMENTS	PROCESS	CHECKS
Inspection table, Containers SS tray, Weighing balance (200 Kg),	<p>Visual Inspection</p> <ul style="list-style-type: none"> Inspect all coated tablets manually and pass the inspected tablets parallelly through metal detector. Transfer the inspected tablets with proper labelling in inspection quarantine area. 	<ul style="list-style-type: none"> Ensure Area cleanliness before starting the activity. Ensure Temperature, % RH and differential pressure of area is within limit. Ensure cleanliness of containers, Equipments and Instruments. Ensure Qualification, calibration & preventive maintenance status of Equipments and Instruments. AQL after completion of inspection. To be sampled as mentioned in sampling plan.

CONCLUSION:

The manufacturing process of Sevelamer Hydrochloride film coated tablets, 800 mg carried out as per the MBMR and Process validation protocol. Which include sifting, blending, compression and coating. All the material used for the manufacturing of tablets were tested as per the given specification and the results were within the limits. → Process is designed by the Quality Assurance in protocol, Production has to adhere to the requirements of the protocol, Quality Control has to analyse the sample and sent report to Quality Assurance department. All the equipments used in the manufacturing of the Sevelamer Hydrochloride film coated tablets, 800 mg were checked for its Installation, operational and performance qualification. Blending time of Raw material at 08 RPM for 30 minutes and Blending time with Lubrication material at 08 RPM for 08 minutes concluded as validated. The granulation process i.e. Dry granulation in place of wet granulation process was validated for Sevelamer

Hydrochloride film coated tablets, 800 mg. All the three batches resulted in granules with desired flow and compaction which is evident from the data of compressed tablets. At compression stage Weight parameters and Speed parameters evaluated and found within Specified limit as well as, The Statistical analysis process performance is high capable, Data is normal and Z bench value also give assurance that process remains in state of control (Process validation state) during manufacturing of Sevelamer Hydrochloride film coated tablets, 800 mg.

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