PROCESS VALIDATION PROTOCOL

FOR

CIPROFLOXACIN HYDROCHLORIDE

EYE DROPS BP 0.3% (5 ml)

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PROTOCOL CONTENTS

PROCESS VALIDATION PROTOCOL FOR CIPROFLOXACIN HYDROCHLORIDE EYE DROPS BP 0.3% (5 ml)

1.0 PROTOCOL APPROVAL

PREPARED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OFFICER/EXECUTIVE (QUALITY ASSURANCE)			

REVIEWED BY:

DESIGNATION	NAME	SIGNATURE	DATE
EXECUTIVE/MANAGER (QUALITY ASSURANCE)			
HEAD (QUALITY CONTROL)			
HEAD (MICROBIOLOGY)			
HEAD (PRODUCTION)			
HEAD (ENGINEERING)			

APPROVED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY ASSURANCE)			

PROCESS VALIDATION PROTOCOL FOR CIPROFLOXACIN HYDROCHLORIDE EYE DROPS BP 0.3% (5 ml)

2.0 OBJECTIVE:

- The objective of this protocol is to validate the manufacturing process of Ciprofloxacin Hydrochloride Eye Drops BP 0.3% (5ml) using qualified facilities, equipment & utilities by evaluating the consecutive batches being manufactured at the Three Piece Line.
- This study shall be conducted for the generation of sufficient data to establish documentary evidence that the manufacturing process including dispensing, CIP/SIP, bulk preparing, filtration, filling, sealing, visual inspection and packing process is suitable and appropriate for its intended purpose and validated process shall consistently meet the predefined specifications and quality attributes of the finished product.

3.0 SCOPE:

- The scope of this protocol is to validate the manufacturing process of Ciprofloxacin Hydrochloride Eye Drops BP 0.3% (5ml) manufactured at Three Piece Line.
- **Type of validation:** Concurrent Validation

4.0 RESPONSIBILITY:

DEPARTMENT	RESPONSIBILITIES
Quality Assurance	1. Responsible to prepare, review and approved process validation protocol. 2. To co-ordinate with cross functional teams to support the process validation execution and also responsible to monitor the execution of process validation. 3. Ensure that the facility/equipment's/instruments and utilities conform to the validated/calibrated state prior to the execution of process validation. 4. To review the trends/statistical evaluation for Critical Process Parameters (CPP)/ Critical Quality Attributes (CQA) for every product manufactured at the site.
IPQA	1. To perform Process validation sampling as per sampling plan and submit them to Quality Control Department. 2. To monitor, verify and record critical process attributes. 3. To record and report any deviation either planned or unplanned happened during batch manufacturing.
QC	1. Responsible to review process validation protocol. 2. To analyze the samples as per sampling plan during process validation and to maintain the records of the test results followed by the reporting of the results. 3. Review of analytical data & submission of analytical results to QA.

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DEPARTMENT	RESPONSIBILITIES
Microbiology	1. Responsible to review process validation protocol. 2. Responsible to collect sample as per process validation protocol. 3. To analyze the samples as per sampling plan during process validation and to maintain the records of the test results followed by the reporting of the results. 4. Review & submission of results to QA.
Production	1. Responsible to review process validation protocol. 2. Ensure that the current effective version of SOP's, Batch Records etc. are implemented and Concerned Personnel are trained. 3. Prior to execution of process validation batch to ensure that facility / equipment / instruments & utilities are in validated / calibrated state. 3. Execution of process validation and collection of routine in-process samples as defined in the batch manufacturing record.

5.0 VALIDATION APPROACH:

Validation shall be carried out in three consecutive batches with prospective approach as new product is introduced to the facility. Study shall be carried out in two phases

- Review of documents.
- Manufacturing of batches.

Review of documents shall include

- Standard Operating & cleaning Procedures & Qualification and Validation status of equipment and system.
- Manufacturing Process & BMR.
- Standard Testing Procedure.
- Raw material, packing material, in-process, finished product specifications.

6.0 REASON FOR VALIDATION:

- New Product manufactured at Three Piece Vial Line.

7.0 REASON FOR REVALIDATION:

- Any major change in the manufacturing process which may affect the quality of the product.
- Any change in the batch size.
- Any change in the batch formula.
- Change in manufacturing site.
- Any modification in any critical equipment.
- Any major modification in the related utility system.
- Any change in the specification and/or change in the source of active pharmaceutical ingredient (API).

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8.0 PRE-REQUISITE:

8.1 TRAINING DETAILS:

- The validation team shall be approved by Head-QA
- All the personnel involved in the manufacturing and Packing of Validation Batches, Sampling and Testing of Validation Samples should be appropriately trained both in their job related activities and on the process validation protocol by Head-QA.

8.2 PRODUCT INFORMATION:

GENERIC NAME	**:**	Ciprofloxacin Hydrochloride Eye Drops BP 0.3%
LABEL CLAIM	**:**	Composition: Ciprofloxacin Hydrochloride BP Equivalent to Ciprofloxacin ……0.3% w/v Benzalkonium Chloride BP…….....0.006% w/v (As Preservative) Sterile aqueous vehicle ……. q.s.
PACK SIZE	**:**	LDPE, White 5 ml
BATCH SIZE	**:**	100 L / 19607 Nos.
MANUFACTURING LICENSE No. :		……..
SHELF LIFE	**:**	36 Months
MARKET	**:**	Export
DOSAGE FORM	**:**	Eye Drops
DESCRIPTION	**:**	A Clear colorless solution free from foreign particulate matter filled in 5 ml white bottles.
STORAGE CONDITION	**:**	Do not store above 25°C. Store in the original packaging. Do not refrigerate or freeze.

MANFACTURING LOCATION:

8.3 ENVIRONMENT MONITORING:

All environment parameters of critical area as listed shall be verified during execution of the process validation study.

- Passive air sampling/Settle plate monitoring
- Active air sampling/Volumetric air sampling
- Surface monitoring
- Personnel monitoring
- Non-viable particle monitoring
- Pressure differential monitoring
- Temperature & Relative humidity monitoring

8.4 MANUFACTURING PROCESS INSTRUCTIONS:

- **Manufacturing process**: Sequential steps in manufacturing process shall be followed as per the approved current BMR. Process parameters during each unit operation shall be monitored to demonstrate that product meets the acceptance criteria.
- **Raw material**: Raw materials to be used in the manufacturing shall be procured from the approved vendor and shall meet all the specifications in the analysis prior to use. All the raw materials shall have valid certification from quality control lab before use for manufacturing. Containers used in the dispensing of raw materials should be clean and dry. After dispensing of API, it should be stored in air tight container.
- **Primary Packing Materials**: Primary packing materials being used in the manufacturing shall be procured from the approved vendor and shall meet the laid down specification in the analysis prior to use.
- **Secondary & Tertiary Packing Material:** Secondary and Tertiary packing materials being used in the packaging process shall be procured from the approved vendor and shall meet the laid down specification in the analysis prior to use.
- **Bulk Preparing:** Temperature of bulk solution is to be maintained during entire batch manufacturing process. Bulk solution hold in SS 316 L mixing vessel should not exceed 12 hours before filtration and filtered bulk solution hold in SS 316 L holding vessel should not exceed 24 hours before final filtration.
- **Filtration**: Pre-integrity test and post integrity test of 0.2 µ filter shall be done with Bubble Point Test at 20°C to 25°C. Bulk solution filtration and filling should not exceed 24 hours.

- Visual inspection of bottles for any defect like Dirty Vial, Mould defect, Broken Ratchet, surface particles, Improper Sealing, improper fixing of cap & vial without cap etc. shall be performed after capping.

8.5 MANUFACTURING FORMULA:

RAW MATERIALS:

S.No.	Material Code	Ingredients	Specifications	Manufacturer Name	Label Claim	Theoretical Quantity (For 100 L)	Unit
1.		Ciprofloxacin Hydrochloride	BP		0.3% w/v	0.364*	Kg
2.		Benzalkonium Chloride 10% w/v Solution	IH		0.006 % w/v**	0.063**	Kg
3.		Mannitol	BP		---	0.820	Kg
4.		Glacial acetic acid	BP		---	0.900	L
5.		Sodium acetate anhydrous	USP		---	0.300	Kg
6.		Disodium Edetate	BP		---	0.050	Kg
7.		Sodium Hydroxide	BP		---	0.150#	Kg
8.		Hydrochloric acid	BP		---	0.030#	L
9.		Water for Injection	BP		---	q.s.	L

Note 1: ***Material has been calculated with considering the Assay; NLT 98.0% (OAB) & Water Content NMT: 6.7%.

Note 2: **This label claim of Benzalkonium Chloride and quantity has been calculated with considering the Assay NLT 9.5% w/v of BKC solution. BKC solution to be dispensed in Kg with respect to weight/ml.

Note 3: # For pH adjustment only.

PRIMARY PACKING MATERIALS:

S.No.	Material Code	Name of Material	Manufacturer Name	Function	Theoretical Quantity (For 100 Liters / 19607 Vials)	Unit
1.	HPME-00051	Bottle, LDPE, White 5ml		Primary Packing Material	19607	Nos.
2.	HPME-00052	Nozzle, LDPE, Natural 5ml		Primary Packing Material	19607	Nos.
3.	HPME-00053	Caps HDPE, White, 20mm		Primary Packing Material	19607	Nos.

8.6 BATCH DETAILS:

Batch No.	Manufacturing Date	Expiry Date	Shelf Life	Standard Batch Size
			36 months$	
			36 months$	
			36 months$	

Batch details such as batch number, manufacturing date and expiry date shall be recorded during protocol execution.

$ Shelf life is provisional and shall be ascertained based on real time stability data.

8.7 EQUIPMENT QUALIFICATION VERIFICATION:

Ensure all equipment's to be used for the manufacturing must be qualified as per Qualification acceptance criteria. The reference Qualification Documents shall be verified and mentioned in the Process Validation Report. The list of major equipment's used for manufacturing of Ciprofloxacin Hydrochloride Eye Drops BP 0.3% (5 ml) in Three Piece line mentioned below:

S.No.	Name of Equipment/Machine	Make	Equipment ID
1.	Mobile Mixing Vessel		
2.	Holding Vessel		
3.	Filling Machine		
4.	Buffer vessel		
5.	LAF for three-piece line		
6.	Dynamic Pass Box		
7.	Dynamic Pass Box		
8.	Dynamic Pass Box		
9.	Dynamic Pass Box		
10.	Dynamic Pass Box		
11.	Static Pass Box		
12.	LAF For Filtration Room		
13.	Autoclave		
14.	Checkweigher		

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9.0	MANUFACTURING PROCEDURE:
	Dispensing, bulk preparation, filtration, filling & screw capping and visual inspection shall be carried out as per the approved batch manufacturing record. All respective process parameters shall be evaluated as specified in this protocol.
	After each stage of process like bulk preparation, filtration, aseptic filling, the samples shall be tested.
	Test Results and data generated during the process validation study shall be compiled and reviewed at each stage of manufacturing.
	Warehouse shall issue the primary packing materials to production department based on the batch record.
	Machine parts shall be sterilized in Autoclave Bung Processor as per the pre-validated loading pattern.
	After sterilization machine parts shall be unloaded in sterile material unloading area and aseptically transferred to the filling room through mobile LAF and Assemble the accessories aseptically on filling machine as per respective SOP.
	Perform the CIP, SIP, of mobile mixing vessel and holding vessel along with product transfer line.
	Process validation batch of Ciprofloxacin Hydrochloride Eye Drops BP 0.3% (5ml) with a batch size of 100.00 L will be manufactured as per the approved BMR.
	After completion batch manufacturing activity, bulk solution is passed through the 0.2 µ filter from mobile mixing vessel to holding vessel and record the filtration activity in BMR.
	Then bulk solution shall be filtered through 0.2 µ filter installed before the buffer vessel.
	Perform the filter integrity test for 0.2 µm filters before & after filtration.
	The filling machine shall fill the solution in to 5 ml bottles through the manifold, filling pump & filling needles.
	After completion of the batch capping activity, reconcile all materials, yield are calculated and recorded in the batch record.
	Capped bottles are transferred to visual inspection and inspect the bottles as per respective SOP.
	After visual inspection good bottles shall be transferred to packing department.

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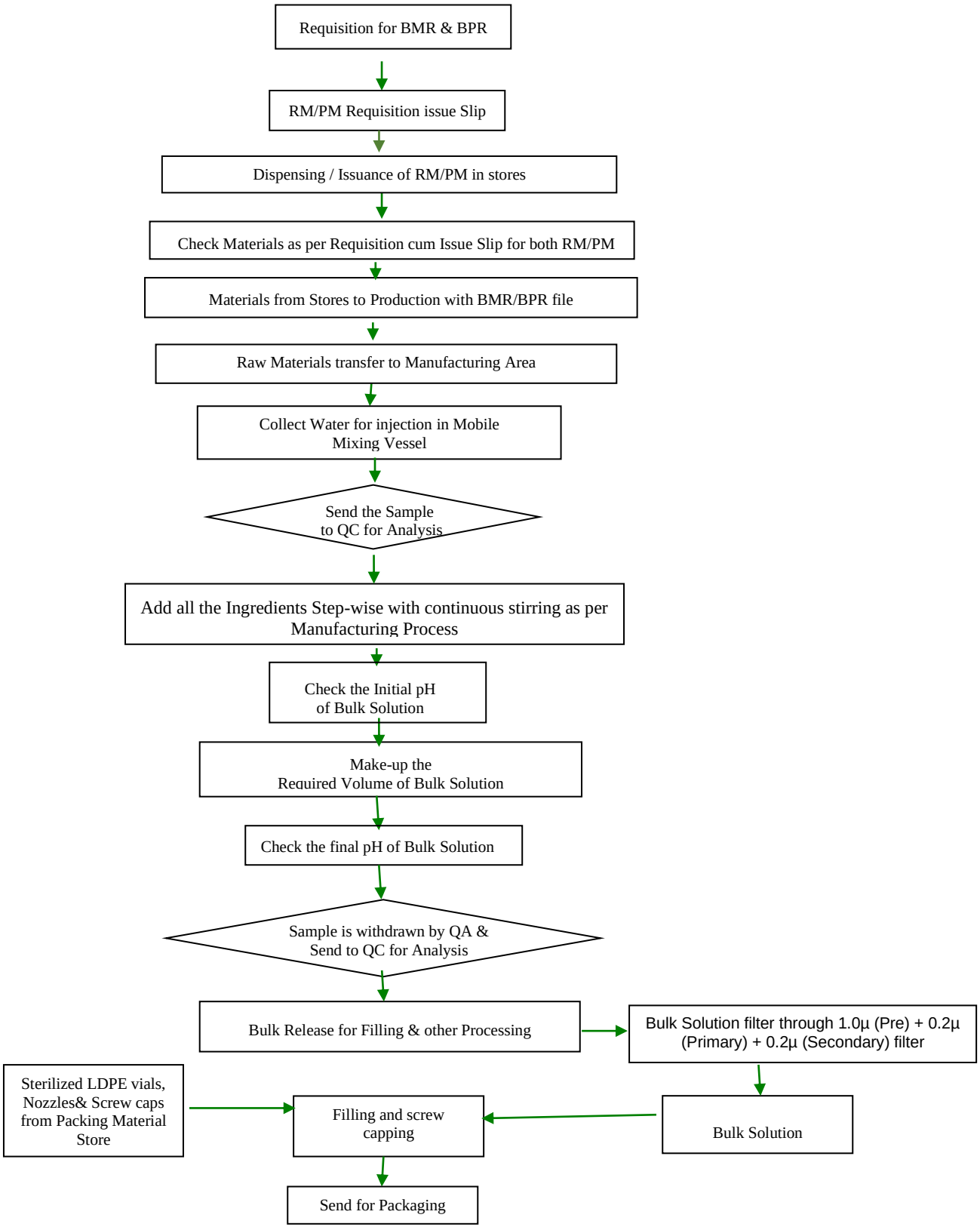
10.0 PROCESS FLOW DIAGRAM:



11.0 DETERMINATON OF CRITICAL PROCESS PARAMETERS (but not limited):

Process Steps	Process Parameters	Rationale	Critical/ Non critical	Assessment Criteria
Dispensing	• Temperature • RH % • Balance Verification	Temperature, RH & Balance Verification is critical and shall be maintained as per API and raw material requirement.	Critical	• Temperature: NMT 25°C • RH: NMT 55% • Should be Complies
Sterilization of Equipment's	• Sterilization time • Sterilization temperature	Sterilization time, Sterilization Temperature is critical and shall be maintained as per Sterility requirement.	Critical	• Sterilization time: NLT 30 Mins. • Sterilization temperature for m/c part: NLT 121.4° C • Sterilization temperature for mobile mixing vessel & holding vessel: NLT 122° C
Preparation of bulk solution	• Load Cell Verification • Temperature • pH • Stirrer speed • Volume makeup	Temperature and pH is critical for stability of formulation. Stirrer speed should be maintained to ensure complete dissolution of API and excipients.	Critical	• Should be Zero • Temperature: 30°C to 40°C • Stirring Speed: 200 RPM to 1440 RPM • pH: 4.0 to 5.0 • 100 L
Filtration	• Filter type • Make • Filter pore size • Filter integrity • Filtration pressure • Filtration Time	Filtration is most critical step to maintain the sterility of the product	Critical	• Sartopore- 2 • Sartorius • 0.2 µ • ≥ 3172 mbar • ≤ 5000 mbar • NMT 2.5 kg • Total Filtration Time
Aseptic filling and Screw Capping of vials	• Filling Speed • Filling machine speed challenge test • Fill Volume verification	Fill volume and filling speed is critical for content uniformity.	Critical	• 80 to 150 vials/min • 5.05 to 5.15 ml • Leak test shall be passed

Process Steps	Process Parameters	Rationale	Critical/ Non critical	Assessment Criteria
	• Bottle, Nozzle & Capping integrity			
Torque Test	• Capping integrity	Cap should be full tight	Critical	• Torque should be pass within specified limit
Labelling Machine	• Machine Speed • Label printing quality	During Bottle Labeling all respective parameters need to be checked for Quality Expects	Non-Critical	• 200 to 300 ampoules/min • Label printing quality & text matter shall be readable
Visual inspection	• Critical, major, minor defects	Removal of defective Vials	Critical	• Visual inspection shall be done as per respective SOP

11.1 HOLD TIME OF COMPONENT:

- Cleaned & sterilized component/garments shall be used within the recommended hold time of respective components and shall be stored under LAF unit.
- Hold time shall be considered from the process end time i.e. cleaning & sterilization upto the uses of components.
- Recommended hold time of various component at different stages is mentioned below.

S.No.	Location	Stage	Component	Recommended Hold Time
1.	Three Piece Line	After Cleaning	Mobile Mixing Vessel	24 Hours
2.			Holding Vessel	24 Hours
3.			m/c Parts	24 Hours
4.		After Sterilization	Sterile Garments	48 Hours
5.			Mobile Mixing Vessel	24 Hours
6.			Holding Vessel	24 Hours
7.			m/c Parts	24 Hours

12.0 SAMPLING AND ANALYSIS PLAN:

Collect the samples at various intervals at different operations as per the Sampling Plan mentioned below.

STAGE	Location of Collection	Test to be performed	Sample size	Responsibility
Cleaning of Equipment's	Mobile Mixing Vessel	Description	100 ML	QA/QC & Production
		Clarity		
		pH		
		Conductivity		
	Holding Vessel	Description	100 ML	
		Clarity		
		pH		
		Conductivity		
	m/c Parts	Description	100 ML	
		Clarity		
		pH		
		Conductivity		
Water for Injection	Before batch mixing	Description	100 ML	QA/QC & Production
		pH		
		Conductivity		
		BET	10 ML	QA/Micro & Production
Preparation of Bulk Solution at 700 RPM	Bulk Mixing after 15 min. (Top)	Description	50 ML	QA/QC & Production
		pH		
		Assay		
	Bulk Mixing after 15 min. (Bottom)	Description	50 ML	
		pH		
		Assay		
	Bulk Sample before Filtration	Description	100 ML	
		pH		
		Weight per ml		
		Colour Index		
		Assay		
		Preservative Content		
		Osmolarity		
		Bioburden	100 ML	QA/Micro & Production
Filtration of Bulk Solution	Bulk sample after filtration	Sterility	100 ML	QA/Micro & Production

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STAGE	Location of Collection	Test to be performed	Sample size	Responsibility
Nitrogen gas from user point	Initial, Middle, End of filling	Sterility	1000 Ltr.	QA/Micro & Production
Pre sterilized empty vial, Dropper, Screw caps	Initial, Middle and End of filling Stage	Sterility	20 Nos. from each stage.	QA/Micro & Production
Filling & Screw Capping	Initial, Middle and End	Description	56 Nos. from each stage	QA/QC & Production
		pH (Acidity)		
		Average filled volume		
		Uniformity of filled volume		
		Particulate Contamination		
		Assay		
		Preservative Content		
		Sterility	20 Nos. from each stage	QA/Micro & Production
Finished Sample	Finish Stage	Description	56 Nos.	QA/QC & Production
		Identification		
		Average filled volume		
		Uniformity of filled volume		
		Osmolarity		
		pH (Acidity)		
		Related Substances		
		Particulate Contamination		
		Assay		
		Preservative Content		
		Sterility	20 Nos.	QA/Micro & Production

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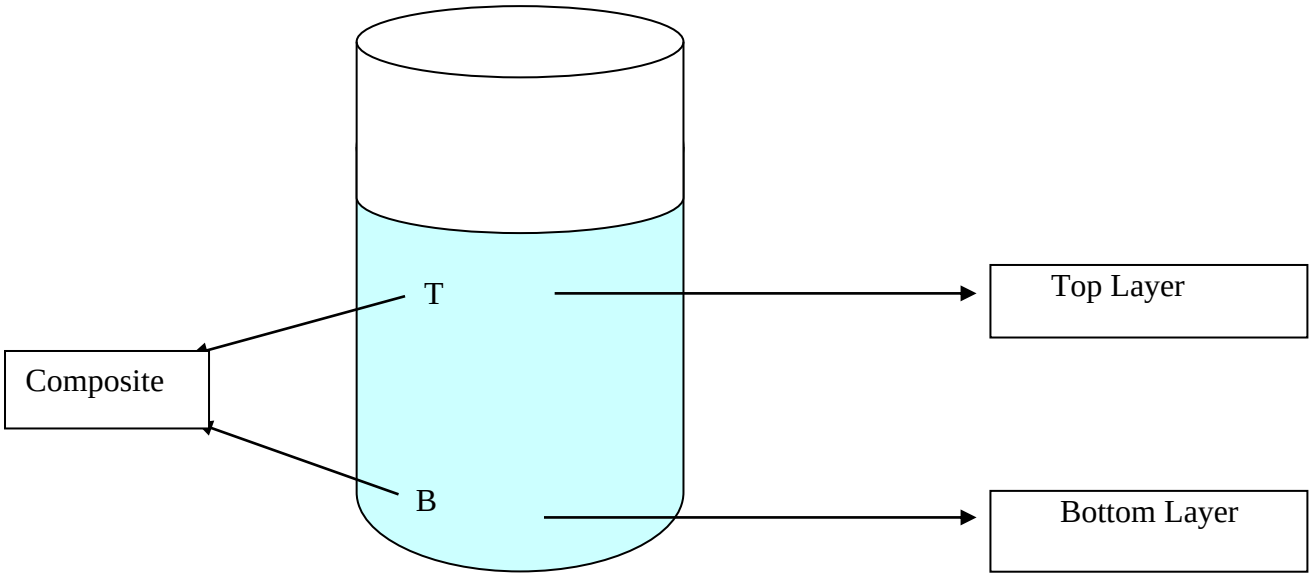
13.0 SAMPLING LOCATIONS:

MIXING VESSEL:



T = Top Layer

B = Bottom Layer

T + B = Composite (Bulk Sample before filtration)

14.0 ACCEPTANCE CRITERIA:

S.No.	Stage	Test	Acceptance criteria
1.	Cleaning of equipment's	**Description**	Clear Colourless Liquid.
		Clarity	Should be clear
		pH	5.0 to 7.0
		Conductivity	NMT 1.3 µS/cm
2.	Water for Injection	**Description**	Clear Colourless Liquid.
		pH	5.0 to 7.0
		Conductivity	NMT 1.3 µS/cm
		BET	NMT 0.25 EU/ml
3.	Nitrogen Gas	**Sterility**	Should be sterile after 14 days of incubation.
4.	Pre sterilized empty vial Dropper, Screw caps	**Sterility**	Should be sterile after 14 days of incubation.
5.	Bulk Mixing	**Description**	A Clear colorless solution.
		pH	4.0 to 5.0
		Weight per ml	0.995 to 1.050 g/ml
		Colour Index	NMT 0.200 AU
		Osmolarity	260mOsmol/kg to 340 mOsmol/kg
		Assay: Each ml contains: Ciprofloxacin Hydrochloride BP eq. to Ciprofloxacin 0.3 %w/v	0.291 % w/v to 0.321 % w/v (97.0 % to 107.0 % of label claim)
		Preservative Content: Benzalkonium Chloride BP 0.006 % w/v	0.00480% w/v to 0.00720% w/v (80.0% to 120.0% of label claim)
6.	Filling and Sealing	**Description**	A clear colorless solution free from foreign particulate matter filled in 5 ml white bottles.

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S.No.	Stage	Test	Acceptance criteria
		Identification	
		A. By HPLC (Diode array detector)	The retention time of the principal peak in the chromatogram obtained with solution (1) should be similar to that of the peak in the chromatogram obtained with solution (2).
		B. By HPLC (Benzalkonium Chloride)	The retention time of the major peak of the sample solution should be corresponds to that of the standard solution obtained as directed in the assay.
		Average filled volume	Not Less Than 5 ml
		Uniformity of filled volume	4.55 ml to 5.45 ml
		Osmolarity	260 mOsmol/kg to 340mOsmol/kg
		pH (Acidity)	4.0 to 5.0
		Related Substance	
		Impurity C	NMT-0.40 %
		Impurity E	NMT-0.30 %
		Any other secondary Impurity	NMT- 0.20 %
		Sum of all secondary Impurity	NMT-0.70 %
		Test for Sterility	Should comply test of sterility.
		Particulate Contamination	
		Visible particles:	Should be free from visible particles
		For sub visible particles:	(i) ≥ 10 micron - NMT 1000 particles/ml (ii) ≥ 25 micron – NMT 100 particles/ml
		Assay: Each ml contains: Ciprofloxacin Hydrochloride BP eq. to Ciprofloxacin 0.3 %w/v	0.285 % w/v to 0.330 % w/v (95.0 % to 110.0 % of label claim)
		Preservative Content: Benzalkonium Chloride BP 0.006 % w/v	For- Information

15.0 CONTINUOUS PROCESS VERIFICATION:

Continuous Process Verification will be carried out for continuous monitoring of manufacturing process both Critical Quality Attributes & Critical Process Parameter as per SOP.

16.0 DEVIATIONS:

All protocol deviation, non-conformances and out of specification results obtained shall be investigated in accordance with corresponding SOP's and documented in the validation report.

17.0 VALIDATION REPORT:

A Validation Report shall be prepared as per the sampling and analysis plan mentioned in this Protocol by Quality Assurance Department. This Report shall be pre-approved by all functional heads of all the concerned departments. Validation data shall be recorded by Quality Assurance Department in the controlled copy of the pre-approved Process Validation Report. This Process Validation Report shall be reviewed and then post-approved by all functional heads of all the concerned departments.

18.0 CONCLUSION:

Validation data shall be written on Process Validation Report, clearly stating the achievement or Non-compliance of the acceptance criteria, effect of the deviations made during the validation and in Case of failure, investigation carried out and their findings.

19.0 REFERENCE DOCUMENTS:

19.1 Relevant Specifications and Standard Testing Procedures

19.2 Relevant Standard Operating Procedures

19.3 Relevant Qualification Documents

19.4 British Pharmacopoeia

20.0 LIST OF ATTACHMENTS:

The relevant following documents to be attached with the Validation Report:

1. Records for all critical parameters with graphical representation, where applicable.
2. Relevant Sterilization Charts
3. Raw Data of Validation Testing.

4. Certificate of Analysis of API.
5. Certificate of Analysis of Finished Product.

21.0 ABBREVIATIONS:

API	: Active Pharmaceutical Ingredient
IP	: Indian Pharmacopoeia
BMR	: Batch Manufacturing Record
BPR	: Batch Packing Record
GMP	: Good Manufacturing Practice
IPQA	: In-process Quality Assurance
NLT/NMT	: Not Less Than/ Not More Than
SOP	: Standard Operating Procedure
STP	: Standard Testing Procedure
w/v	: Weight by volume
BET	: Bacterial Endotoxins Test
CIP	: Clean in Place
SIP	: Sterilization in Place

22.0 REVISION HISTORY:

Revision No.	Change Control No.	Detail of Changes	Reason for Change	Effective Date	Updated By
00		NA	New Protocol		