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Cleaning Validation of Equipments used in Manufacturing of Parenteral in Pharmaceutical Industry

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ABSTRACT

The cleaning validations of three different batches were performed in parenteral production line at Karnataka Antibiotics and Pharmaceuticals Limited, Bangalore.The cleaning validations were performed by evaluating parameters with the acceptance limits. Such as,Major parameters like total residual content, TOC analyzing, microbial count etc.Minor parameters like pH, conductivity, clarity of solutions, visual inspectionetc.The result of each parameter indicates the satisfactory completion of cleaning validation. It was concluded that the cleaning procedure followed is appropriate and which can maintain the drug residues in intend level as per company requirements.So the next batches, which manufacture on same equipments will free from all contaminations and cross contaminations like previous materials, detergents, microbial residues etc. Results have give the assurance about safety and purity for next batch materials.

INTRODUCTION

Validation is a quality system to ensure that quality is designed into a product or process. The FDA defines the term the validation as “establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce product meeting its pre-determined specification and quality attributes”. Validation is a requirement that has always made sense from both a regulatory and quality perspective. In terms of quality philosophy, validation is defined as prevention-based activity, meaning it is performed to ensure product or process integrity. The rationale being that if more effort is placed on development and validation at the beginning and then there will be no chance for failure during product life. Each company indulged in pharmaceutical manufacturing have an overall policy, intentions and approach to validation, including the validation of production process, cleaning methods, analytical test methods, computerized system and an established validation master plan.

Importance: Validation activity must give some advantages or benefits. Which are as following. Reductionof quality costs. Quality costs are reduced by two ways; Internal failure costs: like rejects, reworks, retests, scrap. External failure costs: like recall, complaints and returns due to quality relatedproblems. Processoptimization.Process optimization means make the process effective, efficient, perfect or useful as possible at minimum costs. Assuranceof quality. Validation is an extension of quality assurance. So, control of the process is necessary to assure product quality. Safety.Validation can also result in increased operationsafety.

MATERIALANDMETHOD

MATERIAL–Ranitidine Hydrochloride

METHOD

product: Ranitidine Hydrochloride (2 ml ampoule) Nextproduct:Metaclopramide (2 mlampoule)

Table 1 Materials and those manufactures used in analysis of Ranitidine HCL.

MATERIALS	MANUFACTURES
Ranitidine HCL	Saraca Laboratories, Hyderabad
Metaclopramide	Vaikunth Chemical Ltd., Ankleshwar
Ammonium Acetate	Qualigens Fine Chemicals, Mumbai
Glacial Acetic Acid	S D Fine Chem Ltd., Mumbai
Sucrose	S D Fine Chem Ltd., Mumbai
Methanol	Merck Specialities Pvt Ltd., Mumbai
Soya Bean Casein Digest Agar Media	Himedia, Mumbai

Table 2Equipments, ID no. and those manufactures used in analysis of Ranitidine HCL.

EQUIPMENTS	ID NO.	MANUFACTURES
Ampoule Filling Machine	SVP/AFM01/009	Petals Ltd.
Processing Reactor	SVP/APV02/015	Adams Ampoule Processing Reactor
Ultra Sonicator	QC/WET1/SONI/029	Flexit Laboratories. Pune
Weight Balance	QC/INS/BAL-1/001	Mettler-AE160. Switzerland
HPLC	QC/INS/HPLC-4/033 LC 2010A HT	Shimadzu. Japan
TOC	QC/INS/TOC/036 TOC-V CPH	Shimadzu. Japan
pH Meter	QC/INS/pH-2/045 pH TUTOR	EutechInstument
Binocular Microscope	QC/MB/BM/002	Olympus. Japan

Incubator	QC/MB/IC/016	Matri

Cleaning Procedure and Collection of Sample Filling machine: (Rinse sample)

- After completion of filling activities, filling machine parts were dismantled and transferred to washing area through hatch. All parts were washed thoroughly (one after the other) using the demineralized water with detergent. Filling machine parts were rinsed with sufficient demineralized water and WFI. Then 15-liter of WFI was collected in stainless steel vessel and all parts of filling machine like piston, silicon tubing, connecting rod, dosing needle etc. were dipped in vessel and sent through the sterilization (HPHV) in to sterile area. After sterilization the vessel was removed in sterile area and entire filling parts were dipped three times in collected WFI. Then WFI was taken in sterilized conical flask and labeled it and sent to quality control for analysis.(Swab sample)
- After cleaning of equipment, product contact surfaces could be swabbed to evaluate surface cleanliness like filling table or cabinets.
- They should not cause degradation of compound. The solvent used for swabbing should provide good solubility for the compound.
- Swab method does not cover the entire equipment. So, the sites are chosen carefully.
- The filling cabinet wall and table surface were cleaned with WFI using clean non-linting wet cloth.
- The drug particle was removed from the floor using non-fiber shedding plastic hand brush.

SamplingPoint

Table: 3 Sampling point of Ranitidine HCL.

Rinse sample (filling machine parts)	Rinse sample	Swab sample
Silicon tubing, connecting rod, dosing needle	Processing reactor	Filling machine table surface

HPLCMethod

It has excellent sensitivity with UV detectors, highly specific in nature, reproducible, automated and organic solvent may be used for swabbing should also not interfere with the analysis.

Mobile phasepreparation:A mixture of HPLC grade methanol (850ml) and 0.1M Ammonium Acetate (150ml) was prepared. The mobile phase was filtered with 0.45 µm and degassed by ultra sonicator.

Preparation of 0.1M ammonium acetate: About 7.71 gm. ammonium acetate was dissolved in 200 ml distilled water. Then 1 ml glacial acetic acid of was added and pH was adjusted between 6.7-7.3. Finally the volume was made up to 1000 ml with distilled water.

Standard solution preparation: 30 mg of Ranitidine HCL standard was weighed and transferred in a 100 ml volumetric flask and dissolved in mobile phase. The volume was made up with mobile solvent. From that 5 ml solution was pipetted out in a 50 ml volumetric flask and made up the volume with mobile phase. (30-ppm solution)

.Dilution factor:30 mg in 100 ml (300 µg / ml) (300 ppm)

5 ml in 50 ml (30 µg / ml) (30 ppm)

Sample solution preparation: Rinse solution (filling machine part), was filtered through 0.45 µm filter and from filtrate 20 µl solution was injected in HPLC and chromatogram was recorded.The swab sample was dissolved in 10 ml of mobile phase and filtered through 0.45 µm filter. From 20 µl solution was injected in HPLC and chromatogram was recorded.

Experimental condition:

Quaternary gradient HPLC with UV detector
Column: - Grace smart RP 18 5µ (250mm x 4.6mm) stainless steel column. Injected volume: - 20 µl
Flow rate: - 1.5 ml / min Detector: - 322 nm

TOCMethod

TOC is widely used in pharmaceutical industries for various purposes.
TOC is determined by oxidation of an organic compound into CO_2.
TOC is used for analysis of detergents, endotoxins, biological media etc.
Here, TOC is used to determine total organic residue in rinse and swab sample.

Standard solutionpreparation:Accurately weighed quantity of USP sucrose RS was dissolved, in reagent water to obtain a solution having a concentration of 1.2 mg of sucrose per liter.
Sample solutionpreparation:Final rinse solution of machine parts was directly analyzed in TOC analyzer.
Acceptance criteria: For rinse solution there should be not more than 500 ppb.

Total MicrobialCount

It was carried out by using soya bean casein digest agar media. (Pour plate method).

Procedure:

A.) 1 ml of rinse sample was added to each of two Petri plates and sterile soya bean casein digest agar media was poured to which previously inactivated or neutralized the effect of bacteriostatic or fungi static which may present in rinse sample solution. Tween and lecithin will inactivate the residue ofdisinfectants.
B.) The medium was allowed to solidify and incubated the plate at 37^0c for 5days.
C.) The result was reported as colony forming units per 100 ml of rinse sample, which gave an estimate of the microbial load on that surface.

Acceptance criteria: Microbial count should be not more than 25 cfu / 100 ml.

Swab RecoveryStudy

This was done to determine the efficiency of swab testing procedure in terms of quantity of drugs recovered from the surface. A known concentration of drug was added to the surface of stainless-steel sheet of about 10 x 10sqcm; and the surface was swabbed by same method as above. A cotton wool buds were soaked in water for injection and used for swab the surface.100 mg of drug was weighed and spread in 10 x10sqcm.Now this was swabbed and placed in the glass container in which it contains 10 ml of water for injection.The content in the container was sonicated for 15 min and the solution was filtered using membrane filter(0.45µ).Now this sample was sent to quality control to estimate the quantity of drugs recovered from the surface.

Equation: $\frac{\text{Avg. area of sample x std. weight x100}}{\text{Avg. area of std.}}$

Acceptance Criteria:Recovery should be not less than 70%. Incase this recovery is not achievable; consistency of recovery should be demonstrated.

Establishment of Acceptance Criteria: An acceptable limit is based on therapeutic daily dose. It is generally used for final product change over API process. A limit was established based according to the following equation.

Maximum allowable carryover: $\mathbf{MACO = \frac{SD \times BS \times SF}{LDD}}$

Where, MACO= maximum allowable carryover LDD=largest daily dose of next product
SD= single therapeutic dose of previous product BS= batch size of next product
SF= safety factor of parenteral

In this case, previous product is Ranitidine HCL 50 mg Next product is Metoclopramide 10 mg
SD= 50 mg

BS= 400,000 ml / 2.104 kg of bulk SF= 1/10000
LDD= 30 mg

$$MACO = \frac{50 \times 400000 \times 1}{30 \times 10000}$$
= 66.66 mg present in 2.104 kg

= 31.68 mg per 1 kg

= 31.68 ppm

Acceptance criteria: There should be not more than 31.68 ppm of Ranitidine HCL in next batch.

RESULT

Product change overfrom
product: Ranitidine HCL (2 ml ampoule) Nextproduct: Metaclopramide (2 mlampoule)

CHROMATOGRAM
HPLCCHROMATOGRAM

KARNATAKA ANTIBIOTICS & PHARMACEUTICALS LIMITED, BANGALORE

ANALYSIS OF RANITIDINE HCL: BLANKSOLUTION

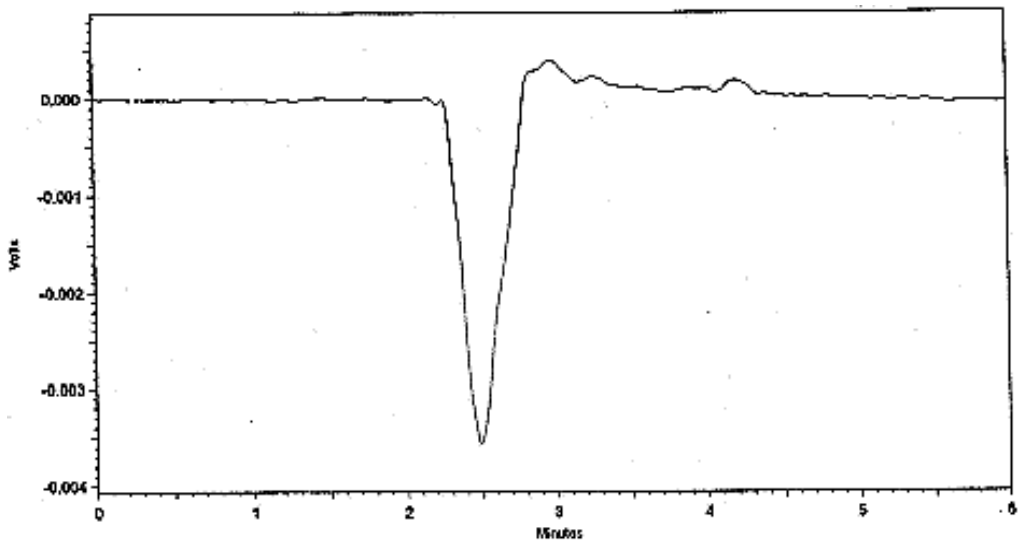


Figure:1 Chromatogram of Blank Solution of Ranitidine HCL.

RANITIDINE HCL: STANDARDSOLUTION

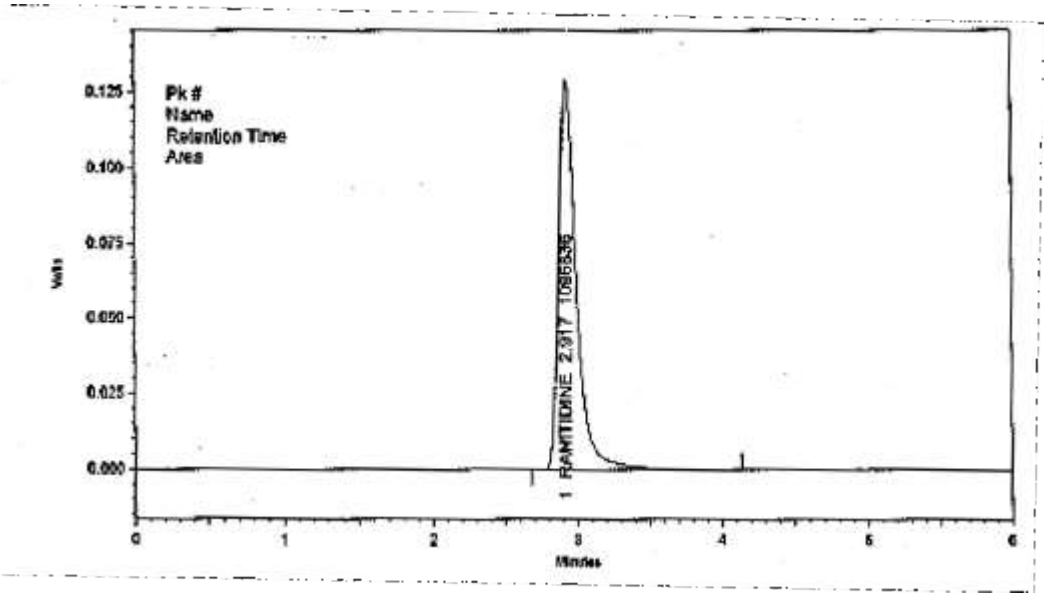


Figure: 2 Chromatogram of Standard Solution of RanitidineHCL.

Table: 4 Summary of System Suitability Parameters of Ranitidine HCL.

No. of injections	Retention time (min)	Area (mV.s)	Theoretical plates	Name	Asymmetry
1	2.892	1087521	3026.88	RanitidineHCL standard	1.44

2	2.900	1089991	2946.99	RanitidineHCL standard	1.52
3	2.917	1098851	2965.06	RanitidineHCL standard	1.53
4	2.917	1095773	2949.56	RanitidineHCL standard	1.53
5	2.925	1097097	2926.47	RanitidineHCL standard	1.48
6	2.925	1100660	2919.53	RanitidineHCL standard	1.48
Avg.	2.912	1094982	2955.75	RanitidineHCL standard	1.50
% RSD	0.470	0.471	1.304	RanitidineHCL standard	2.465

RANITIDINE HCL: RINSE SAMPLE OF FILLING MACHINEPART

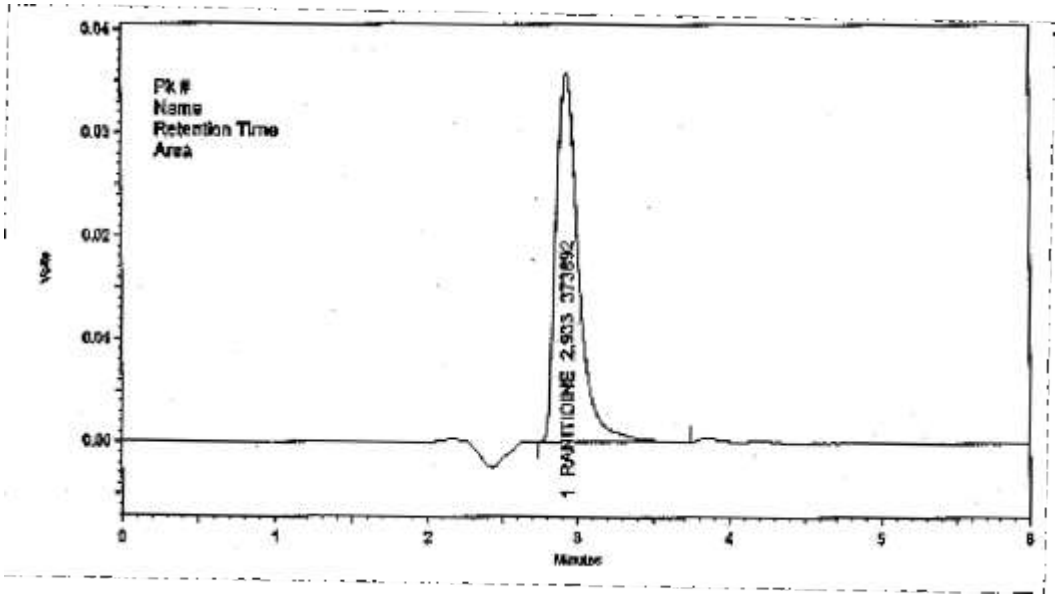


Figure: 3 Chromatogram of Rinse Sample of Filling Machine Part of Ranitidine HCL.

Table: 5 Results of Chromatogram of Rinse Sample of Filling Machine Part of Ranitidine HCL.

No. of injections	Retention time (min)	Area (mV.s)	Theoretical plates	Name	Asymmetry
1	2.933	373892	1978.04	Ranitidine HCL	1.36
2	2.933	373422	2028.87	Ranitidine HCL	1.39
Avg.	2.933	373657	2003.455	Ranitidine HCL	1.375

RANITIDINE HCL: RINSE SAMPLE OF PROCESSINGREACTOR

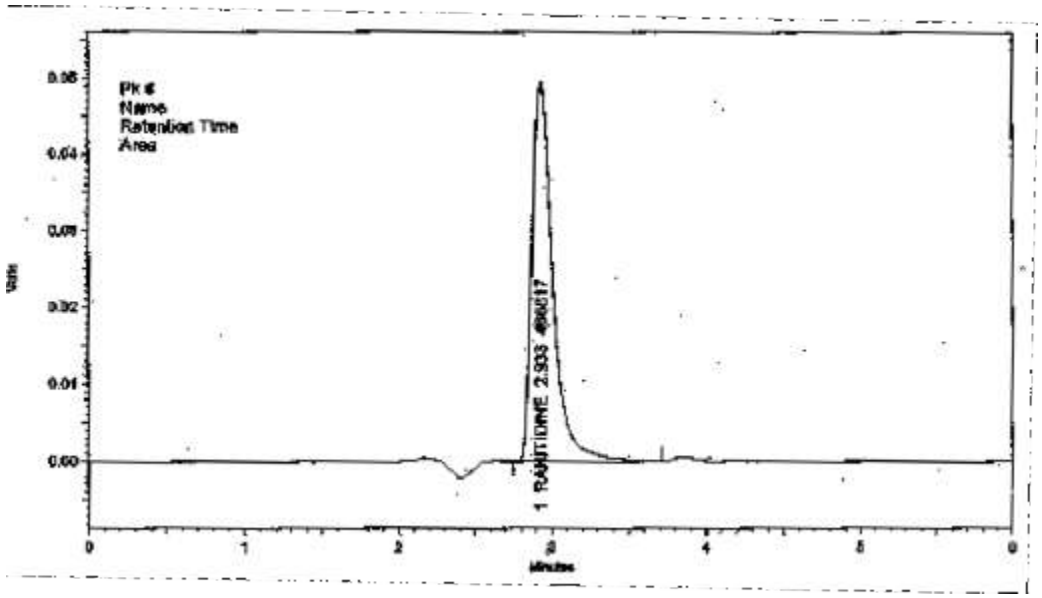


Figure:4 Chromatogram ofRinse Sample of Processing Reactor of Ranitidine HCL

Table: 6 Results of Chromatogram of Rinse Sample of Processing Reactor of Ranitidine HCL.

No. of injections	Retention time (min)	Area (mV.s)	Theoretical plates	Name	Asymmetry
1	2.933	466817	2482.95	Ranitidine HCL	1.50
2	2.925	466813	2437.55		1.62
Avg.	2.929	466815	2460.25		1.56

RANITIDINE HCL: SWAB SAMPLE OF FILLING MACHINE TABLE

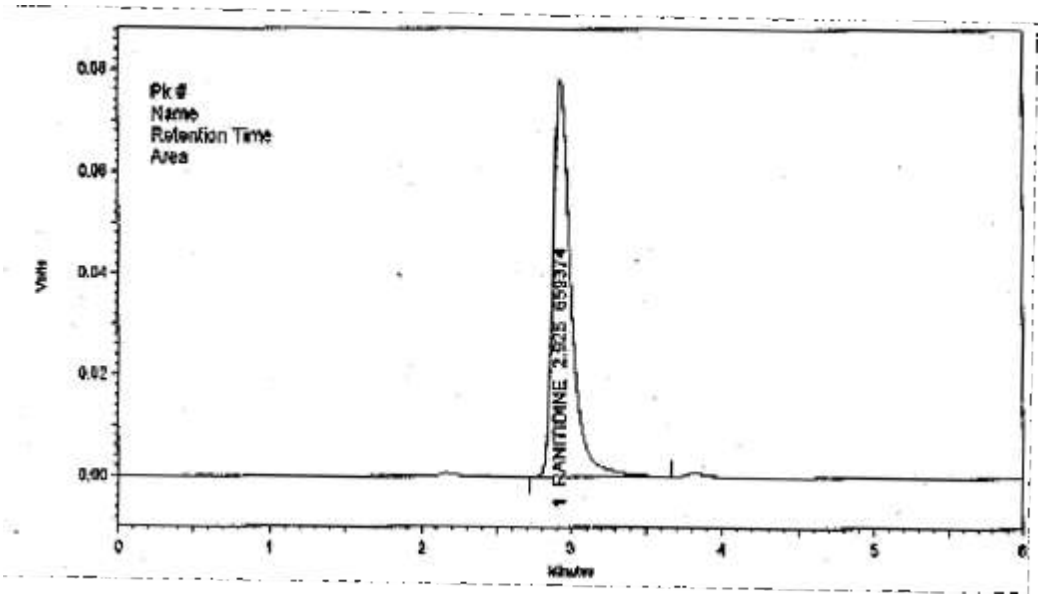


Figure: 5 Chromatogram of Swab Sample of Filling Machine table of Ranitidine HCL.

Table: 7 Results of Chromatogram of Swab Sample of Filling Machine table of Ranitidine HCL.

No. of injections	Retention time (min)	Area (mV.s)	Theoretical plates	Name	Asymmetry
1	2.925	659374	3012.67	Ranitidine HCL	1.56
2	2.925	662907	3111.71	Ranitidine HCL	1.49
Avg.	2.925	661140.5	3062.19	Ranitidine HCL	1.525

RANITIDINE HCL: SWAB RECOVERY PERCENTAGE OF STANDARD

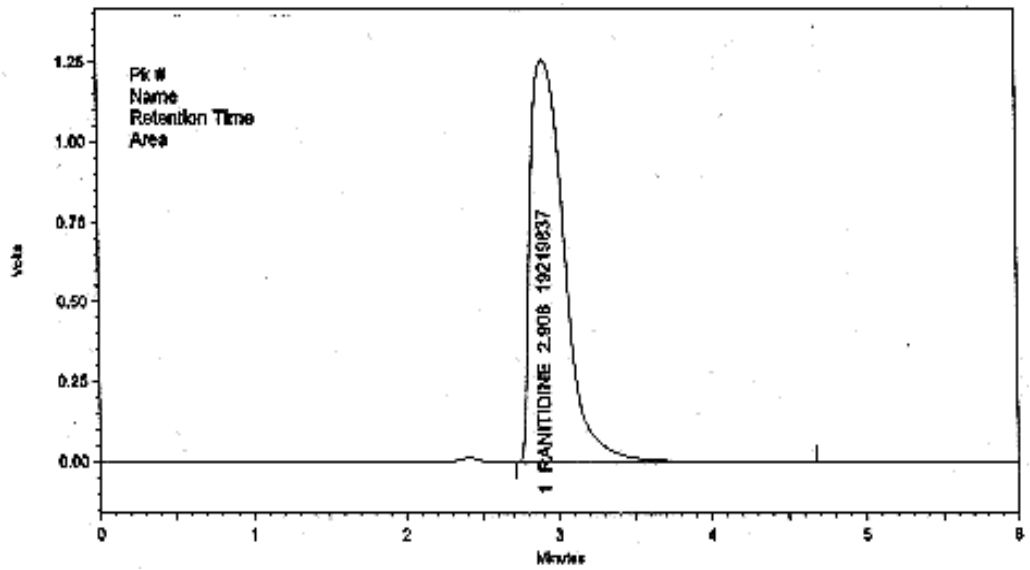


Figure:6 Chromatogram of Swab Recovery Percentage of Standard Ranitidine HCL.

Table: 8 Results of Chromatogram of Swab Recovery Percentage of Standard Ranitidine HCL.

No. of injections	Retention time (min)	Area (mV.s)	Theoretical plates	Name	Asymmetry
1	2.908	19219837	1038.53	Ranitidine HCL	1.81
2	2.900	18758038	1053.95		1.91
Avg.	2.904	18988937.5	1046.24		1.86

RANITIDINE HCL: SWAB RECOVERY PERCENTAGE OFSAMPLE

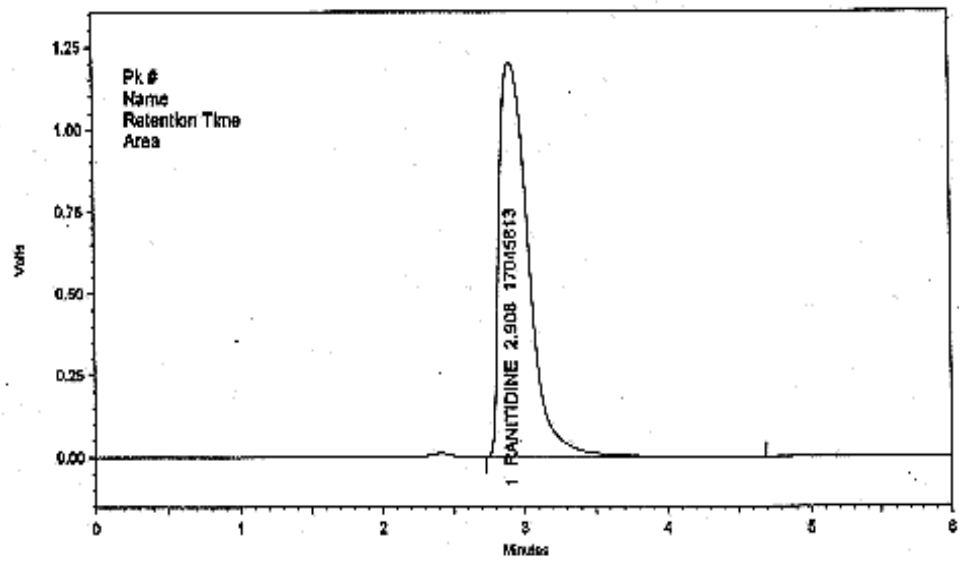


Figure: 7 Chromatogram of Swab Recovery Percentage of Sample.

Table: 8 Results of Chromatogram of Swab Recovery Percentage of Sample Ranitidine HCL.

No. of injections	Retention time (min)	Area (mV.s)	Theoretical plates	Name	Asymmetry
1	2.908	17045813	1171.00	Ranitidine HCL	1.81
2	2.900	17971587	1109.38		1.90
Avg.	2.904	17508700	1140.19		1.855

TOC ANALYSIS: ANALYSIS OF RANITIDINEHCL

Sample

Sample Name: BLANK
Sample ID: WATER
Origin:
Status Completed
Chk. Result

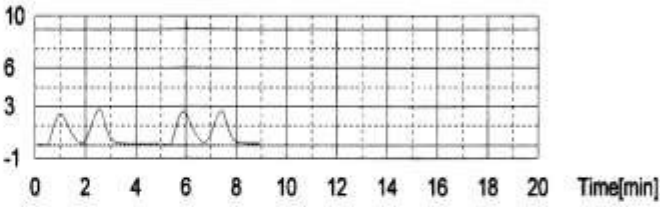
Type	Anal.	Dil.	Result
Unknown	NPOC	1.000	NPOC:0.000ppb

1. Det

Anal.: NPOC

No.	Area	Conc.	Inj. Vol.	Aut. Dil.	Ex.	Cal. Curve	Date / Time
1	20.35	0.000ppb	816uL	1			22/9/2010 6:20:23 PM
2	20.61	0.000ppb	816uL	1			22/9/2010 6:27:09 PM

Mean Area 20.48
Mean Conc. 0.000ppb



Cal. Curve

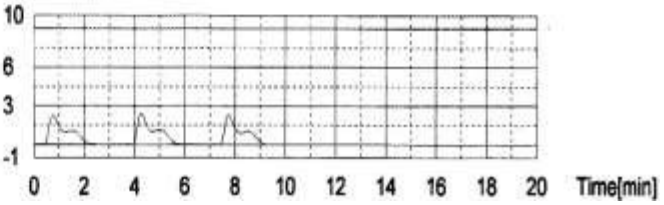
Sample Name: SUCROSE
Sample ID: CALIBRATION
Cal. Curve: suc calib 092210.2010_22_09_13_48_05.cal
Status Completed

Type	Anal.
Standard	NPOC

Conc: 0.000ppb

No.	Area	Inj. Vol.	Aut. Dil.	Rem.	Ex.	Date / Time
1	11.11	816uL	1	*******		22/9/2010 1:55:41 PM
2	11.52	816uL	1	*******		22/9/2010 2:01:55 PM
3	10.65	816uL	1	*******	E	22/9/2010 2:08:05 PM

Acid Add. 0.5000%
Sp. Time 90.00sec
Mean Area 11.32



Type	Anal.	Dil.	Result
Unknown	NPOC	1.000	NPOC:377.6ppb

1. Det

Anal.: NPOC

No.	Area	Conc.	Inj. Vol.	Aut. Dil.	Ex.	Cal. Curve	Date / Time
1	27.61	366.8ppb	816uL	1	E	suc calib 092210.2010_22_09_13_48_05.cal	22/9/2010 3:45:43 PM
2	28.59	379.8ppb	816uL	1		suc calib 092210.2010_22_09_13_48_05.cal	22/9/2010 3:52:05 PM
3	28.26	375.4ppb	816uL	1		suc calib 092210.2010_22_09_13_48_05.cal	22/9/2010 3:58:29 PM

Mean Area 28.43
Mean Conc. 377.6ppb

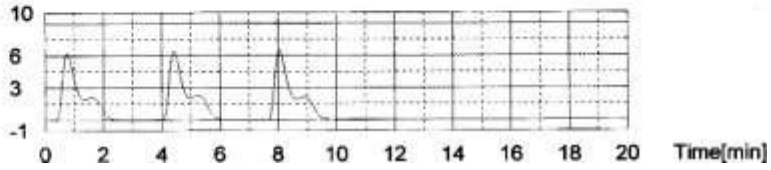


Figure: 8 TOC Report of Ranitidine Sample

Table:9 EVALUATED PARAMETERS WITH ACCEPTANCE LIMITS AND OBTAINED RESULTS OF RANITIDINE HCL

Sr. No.	Test conducted	Acceptance criteria	Result
1.	Visual inspection of cleaned parts.	No powder should be present.	No powder was seen on clean machine parts.
2.	Clarity of final rinse solution.	Rinse solution should be clear, free from fiber and extraneous matter.	Rinse solution was clear, free from fiber and extraneous matter.
3.	Traces of detergent inrinse solution.	Should be absent.	Absent.
4.	pH of final rinsesolution.	Between 6 to 8.5	pH of finalrinse solution was7.4
5.	Residual content in ppm. Rinse sample of filling machine part. Rinse sample of processingreactor. Swab sampleof filling machine table.	NMT 31.68ppm NMT 31.68ppm NMT 31.68ppm	09.17 ppm 11.46 ppm 16.24 ppm
6.	Total microbial count. -Rinse and swab sample.	NMT 25 CFU / 100 ml	8 CFU / 100 ml
7.	TOC ofRinse sample of filling machine part. Rinse sampleof processing reactor.	NMT 500ppb NMT 500ppb	368.8ppb 377.6ppb
8.	Swab recovery percentage.	NLT 70 %	92.20 %

SUMMARY AND CONCLUSION

Cleaning validation studies were carried out at Karnataka Antibiotics and Pharmaceuticals Limited, located in Bangalore. In parenteral manufacturing unit, the three different product's cleaning validations were done. All the results were within acceptance limits as shown below.

Product change overfrom

product: Ranitidine Hydrochloride (2 ml ampoule) Nextproduct Metaclopramide (2 mlampoule)

Table: 10 Tests to be conducted, acceptance criteria and obtained results of product change over from Ranitidine HCl to Metaclopramide.

Sr. No.	Test conducted	Acceptance criteria	Result
1.	Visual inspection of cleaned parts.	No powder should be present.	No powder was seen on clean machine parts.
2.	Clarity of final rinse solution.	Rinse solution should be clear, free from fiber and extraneous matter.	Rinse solution was clear, free from fiber and extraneous matter.
3.	Traces of detergent inrinse solution.	Should be absent.	Absent.
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6.	Total microbial count. -Rinse and swab sample.	NMT 25 CFU / 100 ml	8 CFU / 100 ml
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So the next batches, which manufacture on same equipments will free from all contaminations and cross contaminations like previous materials, detergents, microbial residues etc. Results have give the assurance about safety and purity for next batch materials.

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