Available online on www.ijpqa.com
International Journal of Pharmaceutical Quality Assurance 2015; 6(4); 100-108

ISSN 0975 9506

Research Article

Path Finder Process Validation of Dry Heat Sterilizer in Parentral Manufacturing Unit.

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ABSTRACT
Sterile products have several unique dosage form properties, such as freedom from microorganisms, freedom from pyrogens, freedom from particulates, and extremely high standards of purity and quality; however, the ultimate goal in the manufacture of a sterile product is absolute absence of microbial contamination. Dry Heat Sterilization method is use for Depyrogenation of Glassware (Ampoule, Vial), Metal Equipment, Heat stable Oils, Ointment, and Powders etc. on based on oxidation of microorganism, Conduction & Convection Method. Equipment utilized to provide the dry heat medium must be validated every half year to ensure the system is able to consistently provide Dehydrogenated or sterile product and meets the quality. Validation should be done by proper planning. The efficiency of any heat treatment is determined by the design and source of the heat. To study must done on Heat distribution, Heat penetration, Bioburden and pyroburden determination and microbial/Endotoxin challenges, Minimize the utility cost and Man hours during sterilization cycle. An attempt have been done in this project work to consider all the suitable Critical and Variable parameters in regards to Heat Penetration and Least Temperature required for Sterilization and cost saving.

Keywords:- Dry heat Sterilization , Process Validation , Critical and Variable parameters.

INTRODUCTION

Validation manufacturing processes has always been important in pharmaceutical quality Assurance, recent emphasis on their documentation by the FDA has resulted in a more careful look at the implementation of validation procedures. The process validation Define as ‘’a documented program which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes’’[1]. The principles of qualification and validation which are applicable to the manufacture of medicinal products. It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations[2].

Types of Validation[3]

1. Prospective validation
2. Concurrent validation
3. Retrospective validation
4. Revalidation

The Aim of a sterilization process is to destroy or eliminate microorganism which are present on or in an object or preparation, to make sure that this has been achieved with an extremely high level of probability and to assure that the object or preparation is free from infection hazard[4]. “Sterilization is a term referring to any process that eliminates or kills all forms of microbial life, including transmissible agents such as fungi, bacteria, viruses, spore forms, etc. present on a surface, contained in a fluid, in medication, or in a compound such as biological culture media”[5].

METHODS OF STERILIZATION

Aim and Objective

The main objective of this product is to validate the Dry Heat sterilizer in Parenteral manufacturing unit of Vital Healthcare, MIDC, Satpur, Nashik and suggest cost Effective sterilization process. Study of use Experimental work Sterilization cycles for Accessories and Terminal sterilization according to review study. And also check the critical as well as variable study.

Sterilization

According to Experimental work we found following advantages

Improve sterilization. Reduces the visual rejection because of visual particle. Consumption of electricity.Time saving process. Easy for operation. Reduce Man Hours.

Dry Heat Sterilization

Principle

The killing of microorganisms by heat is a function of the time temperature combination used. If the temperature is increased then the time required for killing all the bacteria will be decreased. Dry Heat sterilization should be used to sterilize anhydrous (waterless) items that can withstand high temperatures.

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Condition: Cycles recommended as per IP[6], BP[7], and USP[8,9] are:

Mechanism of killing the bacteria

The vital constituents of cells such as proteins (enzymes) and nucleic acids are denatured by oxidation. Convection Heating Process the heat transfer through a medium by motion of it‘s parts. Conduction is accomplished ether by a molecular interaction from higher energy level to a lower energy level or by free electrons. Radiant heating is the process which energy flows from high temperature body to a lower temperature[11].

Validation testing[12]

Validation testing must be done in two parts. Heat Distribution Study. Heat penetration Study.

Heat Distribution[13]

This study has traditionally been considered a critical aspect of sterilizer qualification. The intent of this study is to demonstrate the temperature uniformity and stability of the sterilizing medium throughout the sterilizer. Temperature distribution studies should initially be conducted on the empty camber. Temperature uniformity may be influenced by the type, size, design, and installation of the sterilizer. Satisfactory empty chamber temperature uniformity should be established by the User Requirements. A narrow range is required and is generally acceptable if the variation is less than $\pm 1^0$C ($\pm$ 2^0F) the mean chamber temperature. Sterilizers to be used for terminal sterilization of products utilizing a bioburden or BB/BI cycle approach may require enhanced temperature uniformity. In these cases, the sterilizer may be specified to maintain a uniformity of$\pm 0.5^0$C ($\pm 1^0$F) of the mean or even better.

There are two types

Empty chamber testing (Heat Distribution Study).Loaded chamber testing (Heat distribution Study).

Empty Chamber Testing

Heat distribution of an empty chamber

During installation Heat distribution studies are done 3 times. For Revalidation it must be done once. At least 08 RTDs must be placed at different location in the chamber. One RTD must be at least 100 mm away from the sidewalls of Chamber.

One RTD must be placed at the hot air supply point and one near exhaust Point. No RTD must touch any metal surface or the wall of the chamber. Cycle must run at normal parameter of 180^0 C / 90 minutes and Temperature from all probes must be recorded with a time interval of every Five minutes. The temperature of all probes must not vary with the average Temperature By more than 4^0C. The empty chamber cycle is taken the cold spots are determined.

Loaded Chamber Testing

Loaded Chamber Testing Must Be Done In Two Parts.

Heat Distribution

Three cycles must be taken of each testing. (For revalidation only one cycle is taken). Maximum load. Minimum load. Half of temperature probes sensing RTDs are placed near the Ampoules / vials and the rest are suspended at different locations in Dry Heat Sterilizer chamber. Configuration is drawn showing RTDs position. Cold spots are recorded and marked in the loading diagram.

Heat Penetration Studies

This is the most critical component of the entire validation process. The success of a validated cycle depends on determining the F_h value of the cold spot inside the commodity located at the cool spot previously determined from heat distribution studies. The container cold spot for containers $\geq$100 ml is determine container mapping studies. Thermocouple probes are inserted within a Tray of Ampoule/vial and repeat cycles are run to establish the point inside the Tray of Ampoule/vial that is coldest most of the time. It is this exact point that is monitored during heat-penetration studies. Again, the minimum and maximum loading configurations should be studied. Thermocouples will be placed both inside and outside the Tray of Ampoule/vial at the cool spot location, in the. The F_h value will be calculated based on the temperature recorded by the thermocouple inside the container at the coolest area of the load. Upon completion of the cycle, the F_h value will indicate whether the cycle is adequate or if alterations must be made. Following the attainment of the desired time temperature cycle, cycles are repeated until the user is satisfied with the repeatability aspects of the cycle validation process. The operating parameters maintained are 180^0c / 90 minutes. At least five Biological indicators are placed in each cycle. (Initial & Yearly validation) Spore population of Biological indicators must not be less than 106 per strip. At least five endotoxins indicator vials are placed in each cycle covering all cold spots.The Endotoxins content of each endotoxin vials must not less than 10,000 EU per vial. Each vial after exposure is tested at 1:2 in replicate. The Minimum Log Reduction Of Exposed Endotoxin Indicator Vials Is Determined.

MATERIALS AND EQUIPMENTS

Experimental Work

Planning of Experimental Work as Per Objective of Project Work

We have planned to take up product batch for process validation as per protocol.

Product Name: Menadiaone Injection USP. 10mg/ml, 1ml /Ampoule. (VITA K_3)

Batch No: V15116 Batch Size: 40 Lit.

Critical Parameter

Sterilization:-

Formula: -

F_h Value= $\Delta t \times 10^{(T-Tb)/Z}$

Where,

Δt = Total time required for cycle i.e. 90 min.

T = Average of each Probe temperature.

Tb = Standard temperature for cycle

Z= Death Value i.e. 46.4^0C for Dry heat Sterilization.

$=90 \times 10^{(180.95-180)/46.4}$

$=90 \times 10^{(0.95)/46.4}$

$=90 \times 10^{(0.020)}$

=94.24 Min.

MOD ID-001 BATCH NO: V15116 BACH SIZE: 40 LIT 17:00:12 01.
Accessories load 180^{0}C for 90 min

TIME	CH-01	CH-02	CH-03	CH-04	CH-05	CH-06	CH-07	CH-08
17:00:12	35.3	34.4	36.6	36.8	34.3	38.6	36.2	35.8
17:05:12	45.0	56.8	64.1	58.3	54.9	63.4	68.4	64.3
17:10:12	57.3	84.9	83.3	89.7	84.3	83.6	90.5	83.2
17:15:12	66.7	104.5	95.5	108.2	104.5	104.9	103.5	106.2
17:20:12	115.7	112.2	111.7	115.7	112.1	114.4	116.2	116.5
17:25:12	139.6	131.6	125.4	138.4	132.6	121.6	136.6	132.2
17:30:12	145.7	144.9	130.6	148.5	142.1	137.2	144.2	145.5
17:35:12	153.3	150.5	148.8	153.4	157.6	145.8	152.3	154.6
17:40:12	160.5	156.6	159.6	160.2	164.3	156.5	159.3	165.8
17:45:12	164.2	168.4	163.4	168.3	169.3	163.1	164.2	170.2
17:50:12	172.5	171.5	170.3	174.4	173.3	169.4	172.8	174.2
17:55:12	176.3	177.8	177.6	178.5	176.5	174.5	179.5	178.2
18:00:12	180.6	180.9	180.5	180.8	180.5	180.4	180.3	180.7
18:05:12	180.5	180.4	180.4	180.5	180.6	180.3	180.4	180.8
18:10:12	180.6	180.5	180.0	180.4	180.8	180.5	180.3	180.8
18:15:12	180.7	180.7	180.6	180.6	180.9	180.3	180.5	180.6
18:20:12	180.5	180.6	180.5	180.1	180.5	180.1	180.7	180.7
18:25:12	180.8	180.5	181.9	180.7	180.4	180.5	180.6	180.9
18:30:12	180.9	180.4	181.2	180.4	180.4	180.5	180.2	180.8
18:35:12	180.4	180.8	181.7	180.6	180.7	180.2	180.1	180.8
18:40:12	180.7	181.2	181.2	181.5	180.5	180.2	180.4	180.6
18:45:12	181.6	181.4	182.4	181.4	181.9	180.3	180.2	180.9
18:50:12	181.4	181.5	181.8	181.6	181.8	180.2	180.3	180.8
18:55:12	181.6	181.3	181.6	181.4	181.4	180.2	180.5	180.6
19:00:12	181.8	181.4	182.4	181.3	181.7	181.3	180.7	180.6
19:05:12	181.5	181.6	182.2	181.5	180.4	181.1	180.5	180.9
19:10:12	181.4	180.5	181.4	181.6	180.5	180.5	180.2	180.8
19:15:12	180.8	180.8	181.6	181.8	180.4	180.4	180.1	180.6
19:20:12	180.4	180.5	181.3	181.0	180.6	180.3	180.0	180.8
19:25:12	180.7	180.6	180.5	180.3	180.6	180.1	180.3	180.8
19:30:12	180.4	180.5	180.4	180.0	180.4	180.4	180.6	180.8
19:35:12	170.5	173.2	169.3	174.3	165.5	172.5	174.4	173.5
19:40:12	155.2	162.5	149.8	160.6	150.5	162.3	163.8	154.8
19:45:12	120.3	130.1	127.4	143.2	145.5	141.1	151.4	142.5
19:50:12	113.2	110.8	118.1	112.3	120.6	105.5	112.8	117.3
19:55:12	105.5	100.3	99.9	102.5	102.6	95.6	102.5	104.4
20:00:12	92.4	88.4	79.8	78.9	92.2	76.4	85.4	75.4
20:05:12	84.6	69.3	68.6	65.4	76.2	62.5	75.4	67.7
20:10:12	68.8	53.3	52.1	54.2	55.4	55.6	52.3	57.4
20:15:12	52.6	40.9	43.1	46.2	41.8	43.5	43.3	45.5
20:20:12	48.2	35.4	35.5	35.2	32.4	32.1	32.6	34.4
Average =	180.95	180.9	180.84	181.24	180.9	180.6	181.45	

MOD ID-001 BATCH NO: V15116 BACH SIZE: 40 LIT 15:30:15 02/03/2015
Terminal load 160^{0}C for 1Hours

TIME	CH-01	CH-02	CH-03	CH-04	CH-05	CH-06	CH-07	CH-08
15:30:15	65.4	74.6	66.5	62.8	64.3	69.6	66.5	64.2
15:35:15	85.5	96.5	94.6	87.3	84.9	89.5	91.4	84.6
15:40:15	107.6	104.8	103.5	100.7	104.3	103.4	106.2	106.2
15:45:15	132.6	134.6	120.5	128.2	124.5	126.6	129.5	126.3
15:50:15	145.8	142.5	146.4	145.7	142.1	144.4	147.2	146.5
15:55:15	156.2	152.6	156.1	158.4	152.6	151.5	156.6	152.6
16:05:15	160.8	160.8	160.4	160.5	160.1	160.5	160.8	160.5
16:10:15	160.5	160.9	160.2	160.4	160.6	160.2	160.6	160.5
16:15:15	160.6	160.6	160.6	160.2	160.3	160.1	160.4	160.8
16:20:15	160.5	160.6	160.1	160.3	160.3	160.0	160.2	160.5
16:25:15	160.8	160.2	161.2	160.4	160.3	160.4	160.8	160.9
16:30:15	160.9	160.3	161.6	160.5	160.5	161.9	160.5	160.2
16:35:15	160.6	160.2	162.4	161.8	161.5	161.4	161.3	161.1
16:40:15	161.4	161.4	161.2	160.5	161.6	161.7	161.4	161.3
16:45:15	161.5	161.1	161.5	161.4	161.8	161.2	161.3	161.9
16:50:15	161.4	162.5	161.4	161.6	161.9	161.6	161.5	161.5
16:55:15	161.6	161.6	161.6	161.1	161.5	161.4	162.7	161.7
17:00:15	161.5	161.4	161.4	161.7	161.4	161.2	162.6	161.6
17:05:15	152.4	153.4	151.2	155.4	150.4	153.0	152.2	150.4
17:10:15	135.5	140.8	141.0	139.6	140.7	138.2	148.1	142.3
17:15:15	109.2	111.0	118.1	115.5	120.5	109.3	119.4	112.1
17:20:15	91.4	98.4	102.6	96.4	98.9	90.1	102.2	100.3
17:25:15	81.1	78.5	91.5	68.6	65.8	74.2	89.5	90.5
17:30:15	66.0	52.3	78.6	41.4	43.2	54.5	60.8	69.6
17:35:15	41.2	41.4	62.8	35.3	36.6	42.1	51.6	50.9

Less Rejection

Visual rejection for this batch is 1.09%. (limit is below 3%)

Energy Saving

According to Industrial Electric survey found that Rs.14/ unit.

1 Hr 1000 watts = 1unit

1000watt x 40 Heaters= 40 units/ Hr

= 80 units/ 2Hrs

Saving of Man Hours

During sterilization of Ampoule and vials on DHS requires 4 and 8 hours .Each Shift 1persons are engage for DHS loading, Cycle processing, and DHS unloading . Normal Routine one person take Ampoule and vial load cleaning, loading, cycle processing, cooling then unloading Take eight hours and terminal sterilization cycle take 4-5 hours.

= 8hr x4person

=32 hours (08hrsx02 one shift + 08x02 hours second shift.)

After experimental work one cycle six hours and terminal sterilization four hours

=6hr x4 person

=24 hours (One shift 12 hours per ship.)

Save 8 Hours

Breakage during Sterilization

Avoid overheating causes less breakages of Ampoule and vial during sterilization.

Variable Parameter

Time and Temperature

Time is the variable parameter. time depend on the temperature achieve in the chamber in vital cycle 200^0 C temperature is achieve at 1 to 2 hours so the cycle is extended at respected temperature. High heat causes cooling time also extended at respected temperature. experimental cycle 180^0 C cycle is temperature achieve maximum 1 Hours so cooling time also less. time is critical as well as variable parameter because the organism do not die same time so the study of time also important in sterilization.

Cold Spot

Cold spot is the point which probe show low temperature. In Vial DHS cold spot is found near the door. we found that 6 no. probe cold point.

Hot Spot

Hold spot is the point which probe show High temperature. In Vial DHS Hot spot is found Upper side the door. we found that 8 no. as hot Point.

Design of probe placement

Using calibrated temperature probes in vials/ vessels throughout the oven under maximum load. Include probes in the middle of the load. A common minimum 3 probes on the top, middle and bottom shelves. Additional Probes are placed according to equal distance so the better heat penetration and heat distribution study is done.

RESULT AND DISCUSSION

The result observed in the sterilization of batches of Menadione Injection USP 10mg/ml 1ml (VITA K_3) Batch no. V15116 B. Size: - 40 lit prior to process validation set in the project are annexed herewith as per QCM/007/F_1-01.

CONCLUSION

Table No.1:- Method of sterilization.

STERILIZATION METHODS

PHYSICAL			CHEMICAL	MECHANICAL
			Gaseous sterilization With ethylene oxide	Filtration through bacteria proof filter units
Dry heat	Moist heat	Radiation		
i)Heating in hot air oven ii)Flaming iii)Infra-red radiation	i)Moist heat in autoclave ii)Heating with a bactericide iii)Heating at 100^0C iv)Pasteurization v)Tyndalization vi)Heating at 55to 60^0C	i)By exposure to UV - rays ii) By ionizing radiation. (i.e. gamma rays)		i) Berkefeld filter (could be porcelain, keiselguhr) ii)Seitz filter (Asbestos pads) iii) Sintered glass filter iv) Sintered metallic filter v) Membrane filters

Table No. 2: Sterilization cycle

S.No	Loads	As per SOP of Vital Healthcare Pvt. Ltd.	Experimental
1.	Accessories	200 ^{0}C for 2 Hours	180 ^{0} C for 90 minute
2.	Terminal	180 ^{0} C for 90 minute	160 ^{0}C for 1Hours

Table No.3: Cycles recommended as per BP, IP, and USP.

S. No.	Specification	Accessories load		Terminal Load	
		Temperature	Time	Temperature	Time
1.	As per IP 2014	200 ºC	2 hours	180 ^{0}C	90 min
2.	As per IP 2014	180 º C	90 min	180 ºC	NLT 30
4.	As per BP 2014	200 ºC	2 hrs.	160 ºC	1 hrs.
5.	As per USP 2014	160 ºC	2 hours	180 ^{0}C	NLT 1hours

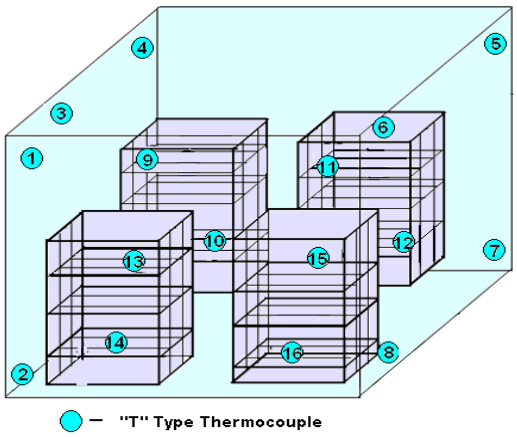

Figure No.1:-Probe location (Heat Distribution study).

Figure No. 2:-Probe Location in Ampoule

Table No. 4:- List of Material.

S. No	Material
1.	Ice pack (For Calibration of RTD Sensor)
2.	Lighter(For Calibration of RTD Sensor)
3.	Teepol solution(20) (Cleaning of Aseptic area)
4.	70% IPA(20) (Cleaning of DHS)
5.	Physical Indicator (Thermo Graph and Printout Of Microprocessor)
6.	Pointer (For Physical Indicator drawing)
7.	Chemical Indicator (Browne's test strip)
8.	Endotoxin Indicator (Bacillus substilis Vials)
9.	Vial/Ampoule loading S. S. Trays
10.	Vial/Ampoule loading Racks
11.	Aluminium Pots (Terminal Sterilization)
12.	Compressed Air (For Cleaning of Vial /Ampoule breakage in DHS)
13.	Floor trolley (Transportation)

Figure No. 3:- Probe Location in Vials

Table No. 5:- List of Equipments.

List of Equipments	
S.No	Equipments
1.	Vial Dry Heat Sterilizer
2.	8 Fixed RTD Probes (Sensitivity ± 0.1 degree)
3.	16 RTD Flexible Probes (Sensitivity ± 0.1 degree) (Techno)
4.	Data Logger (SUNPRO/HMI-075 U)
5.	Incubator (For Microbiological study)

Figure No. 5:- Flexible Probes

Figure No. 6:-Calibration of Probes

This project work was carried out to validate the Dry Heat

INDICATORS

A. Physical Indicator :-Time and temperature recording devices. Thermocouples can be placed inside the load to determine the temperature achieved in the load itself.

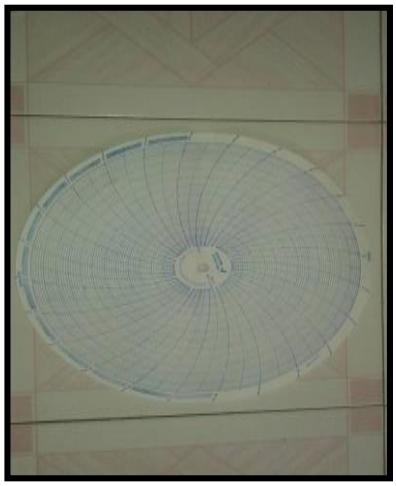

Figure No.7:- Thermo Radix Graph.

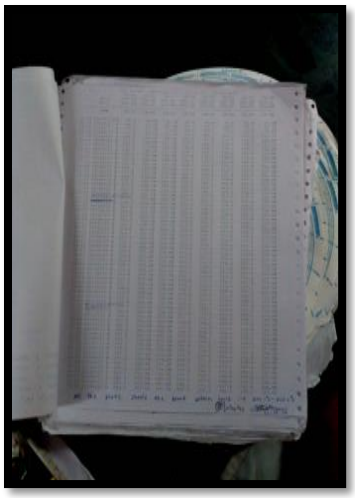

Figure No.8:-Printouts

Figure No.9:-Microprocessor

B.Chemical Indicator:-These indicators change colour after being exposed to specific temperatures.

Figure No.10:- SGM Strips.

Figure No.11:- Browne's tube.

C.Biological Indicator: This is the standard method of validating the effectiveness of your DHS procedures. Testing using a biological indicator must be undertaken monthly. Bacillus subtilis is used for DHS.

Figure No.12:-Biological indicator.

Table No.6:- Sterilization cycle as per protocol.

S. No	Cycle parameter	Sterilization cycle for accessories sterilization.	Sterilization cycle for terminal sterilization.
1.	Time	90 min	60 min
2.	Temperature	180^0C	160^0C

Table No.7:- Experimental work

S. No	Critical parameter	Variable parameter
1.	Sterilization	Temperature, Time
2.	Less rejection	Cold Spot
3.	Energy saving	Hot spot
4.	Man hours saving	Design of probe placement
5.	Breakage during sterilization	-

Table No. 8:- Sterilization cycle

S. No.	Loads	As per SOP of Vital Healthcare Pvt. Ltd.	Experimental
1.	Accessories	200 ^{0}C for 2 Hours	180 ^{0} C for 90 minute
2.	Terminal	180 ^{0} C for 90 minute	160 ^{0}C for 1Hours

Table No. 9:- Result.

Batch	Sterilization conditions Temp/hr	Sterility/ BET Test	Optical/ visual inspection report
Menadione Injection USP 10mg/ml 1ml (VITA K_3) Batch no. V15116 B. Size:- 40 lit	Accessories load 180 ^{0}C for 90 min.	Pass	NA
Menadione Injection USP 10mg/ml 1ml (VITA K_3) Batch no. V15116 B. Size:- 40 lit	Terminal load 160 ^{0}C for 60 min.	Pass	1.09 Limit :- Below 3%

Sterilizer in Parentral Manufacturing Unit. The result found to be good and within targeted limits. It is saving

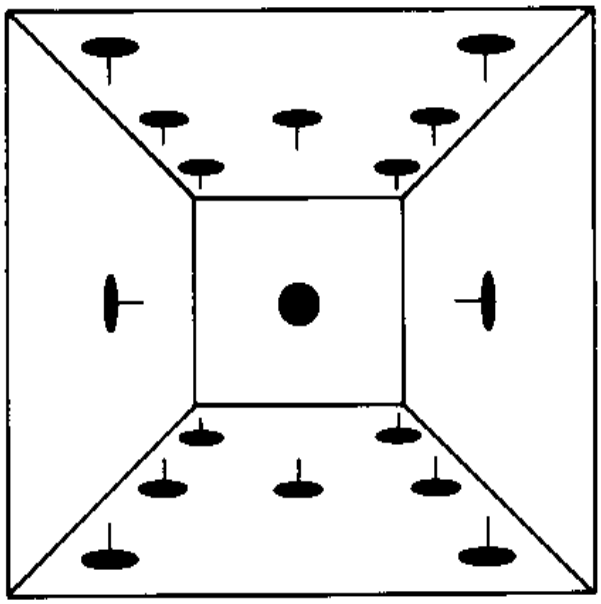

Figure No.13:- Equal Distance distribution of probes/RTD.

Cost through Energy Saving, Man Hour Saving and Breakage of Units. We have also tried to find out Hot and Cold Spots in Dry Heat Sterilizer and Design placement of RTD for Dry Heat Sterilizer of Parentral Manufacturing Unit and suggested all the parameters and findings with the Parentral Department of vital Healthcare Pvt. Ltd. Satpur. MIDC, Nashik. India

REFERENCES

1. Sanford Boltan, Charles Bon, Pharmaceutical Statistics Practical and Clinical Application ,4th edition, volume 135, Marcel Dekker, Inc.New York Basel. pp.416
2. Michael J. Akers Baxter Pharmaceutical Solutions, U.S.A. Neil R. Anderson Eli Lilly and Company, Indianapolis, Indiana, U.S.A. Sterilization Validation 2002, pp.20-28.
3. B .Venkateswarwa Reddy , B.R. Reddy A Review on Qualification of Autoclave , RMG , FBD, Cone blender ,Tablet compression machine , Journal of Globle Trends in Pharmaceutical Sciences .Jan- March 2014. 1-8.
4. Garfinlde Bony PhD ,Martin Henly PhD, Sterilisation ,Remington The science and practice of pharmacy, 19th edition Vol.-II Mack publication ,1995 pp.1463-1465.
5. Hugo and Russell's Pharmaceutical Microbiology edited by Stephan P. Denyer, Norman A. Hodges and Sean P. Gorman , Blackwell publishers 7th edition 2005 pp. 346, 355.
6. Indian pharmacopoeia Volume I, Sterilization, The Indian Pharmacopoeial Commission, Govt. of India, Ghaziabad 2014 pp.565-567.
7. United State Pharmacopeia 20th Convention, Washington D.C 2014, Volume II pp.241.
8. USPXX the United State Pharmacopeia, NFXV the National Formulary2014 Sterilisation pp.1037, 1038, 1040.

Table No. 10:-Critical parameters

Parameter	Load taken	Load Use to take
Critical Parameters considered	Batch-A Menadione Injection USP 10mg/ml 1ml (VITA K_3) Batch no. V15116 B. Size:- 40 lit	Batch –B- Menadione Injection USP 10mg/ml 1ml (VITA K_3) Batch no. V14893 B. Size:- 40 lit
1.Sterilization	1. Accessories load 180 ^{0}C for 90 min. 2.Terminal load 160 ^{0}C for 60 min.	1. Accessories load 200 ^{0}C for 2 Hours. 2. Terminal load 180 ^{0}C for 90 min.
2.Less Rejection	Visual rejection for this batch is 1.09%. (limit is below 3%) i.e. Less rejection.	Visual rejection for this batch is 2.3%.(limit is below 3%) i.e. More rejection.
3.Energy Saving	We reduce our cycle time from 120 min to 90 min, for accessories sterilization. And for terminal sterilization we reduces cycle time from 90 min to 60 min. it means we reduces 30 min in each load. If, 80 units /120 min then, 60 units / 90 min. According to that we saved energy up to 20 units. For load 90 min we spent Rs.840 we save Rs. 280 / cycle.	As per previous cycle, we took accessories load on 200^{0}C for 120 min. and Terminal load on 180^{0}C for 90 min. No energy saving. For load of 2 hours we spent Rs.1120
4.Man Hours Saving	After experimental work we observed that, one cycle of six hours for accessories and 4 hours for terminal sterilization. For accessories sterilization 6hr x4 person =24 hours (One shift 12 hours per ship. Save 8 Hours. for terminal sterilization 4hr x4 person =16 hours (One shift 12 hours per ship. Save 8 Hours.	For 1 load of DHS we require 4 people, and 8 hrs to complete load from loading to unloading of amp/vial. As per regular cycle. For accessories sterilization: 8hr x4person =32 hours (08hrs x 02 one shift + 08 x 02 hours second shift.) For terminal sterilization: 6hr x4person =24 hours (06hrs x 02 one shift + 4 hour.) No man hour saving.
5.Breakage during sterilization	Breakage During Accessories sterilization is 218 Ampoules Breakage During Terminal sterilization is 40 Ampoule. i.e. Less breakage during sterilization.	Breakage During Accessories sterilization is 245 Ampoules. Breakage During Terminal sterilization is 55 Amp. i.e. More breakage during sterilization.

Table No.11:- Variable parameter

Variable Parameters considered	Batch-A Menadione Injection USP 10mg/ml 1ml (VITA K_3) Batch no. V15116 B. Size:- 40 lit	Batch –B- Menadione Injection USP 10mg/ml 1ml (VITA K_3) Batch no. V14893 B. Size:- 40 lit
1.Temperture and time	Cycle parameter, Accessories- 180^{0}C for 90 min. Terminal- 160^{0}C for 60 min.	Cycle parameter, Accessories- 200^{0}C for 120 min. Terminal- 180^{0}C for 90 min.
2. Cold Spot	During the cycle of load, we found that 6 no. probe is cold spot near to the DHS unloading side door.	During the cycle of load, we found that 2 no. probe is cold spot near to the DHS unloading side door.
3.Hot Spot	During the cycle of load, we found that 8 no. probe is hot spot near to the DHS roof.	During the cycle of load, we found that 5 no. probe is hot spot near to the DHS roof.
4.Design of probe placement	We suggest that the Equal Probe distribution. We added 2 more probe as per following fig.	In this load 8 NOS of probe and 1 is graph probe and 1 is Radix.

9. Thomas C. Kupiec, Riaz Ahmad, and Dry-Heat Sterilization of Parentral Oil Vehicles International Journal of Pharmaceutical Compounding Vol.4 (3) May-June 2000, 223.
10. Robert A Nash And Alfred H Wachter, “Pharmaceutical Process Validation” An International, 3rd Edition , Revised and Expanded Volume -129, 2002 ,pp. 95-102.
11. Vital HealthCare Pvt. Ltd. Nashik, DHS Validation SOP no.:- QA/045-02
12. Vital HealthCare Pvt. Ltd. Nashik, Validation Protocol no.:- VP/003/14.

13. Vital Healthcare Pvt. Ltd. Nashik, Cleaning of Dry Heat Sterilizer SOP No.:- PD/095-02
14. Vital HealthCare Pvt. Ltd. Nashik, DHS Sterility Test SOP no.:- QCM/007-02
15. Vital HealthCare Pvt. Ltd. Nashik, DHS Bacterial Endotoxin Test SOP no.- QCM/006-02