STERILIZATION OF PHARMACEUTICALS

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Introduction

- Sterilization is the process of complete destruction of all forms of microbial life in or on the given object or preparation.
- Microbiologically, sterile material is one that contains no living organisms at all.
- Accordingly, an object is sterile or non sterile but it can never be semisterile or almost sterile.

Definitions of term related to sterility

1. Antiseptic: A substance that arrests sepsis i.e prevents the growth of microorganisms by inhibiting their activity without destroying them. These can be applied on human body.
2. Bactericide: An agent that kills bacteria.
3. Bacteriostatic: An agent that arrests or retards the growth of bacteria.
4. Viricide : An agent that kills virus.

5. Disinfection: A process that removes infection potential by destroying microorganisms but not ordinarily bacterial spores.
6. Disinfectants: These are generally meant for application on inanimate objects.
7. Germicides: A substance that kills disease microorganisms (i.e. pathogens / germs) but not necessarily bacterial spores.
8. Sterility: The absence of viable organisms.
9. Viable: Live and growing bacteria (or microorganisms) + spores.
10. Vegetative microorganisms: Growing organisms.

Thermal death time(Minute)

		Autoclaving				Dry Heat			
Organism	**Boiling water**	**115 ^{0}C**	**120 ^{0}C**	**130 ^{0}C**	**120^{0}C**	**150 ^{0}C**	**160 ^{0}C**	**180 ^{0}C**	**Remark**
Nonsporing bacteria, virus, moulds and yeast(including spores)	2	-	1	<+	-	-	3	<1	Highly sensitive
Cl. Prefringes spores	5	-	2	<+	-	-	4	<1	Slightly resistant
Cl. Welchii(spores) B.anthracis(spores)	4-45 2-15	4 -	1 -	- <+	50 180	5 6-120	- 9-90	- 3	Moderately resistant
Cl. Tetani (spores)	5-90	-	5	1	-	30	12	1	resistant
Cl. Botulinum (spores) Soil bateria (spores)	>300 >500	10-40 15	4-20 6-30	2 4	120 -	30 180	20 30-90	5-10 15	Very resistant

Thermal Resistance of microorganism

- Thermal death time : time required to kill a specific microorganism at a given temperature under specific condition.
- Death rate of microorganism: to plot a graph between survivors against time of exposure.
- Decimal reduction time (D value): It is the time in minuets required to reduce the number of microorganisms by 90% and it indicate the efficiency of sterilization process.

Factors affecting the thermal destruction of microorganism

1. ph
2. Protective substances
3. Antibacterial agents
4. Inhibitory medicaments
5. The inactivation factor of the process
6. Initial number of organisms

Methods of sterilization:

1.Physical processes of sterilization.

a. thermal methods

-Dry heat sterilization

-moist heat sterilization

b. non-thermal methods (radiation)

-ultraviolet light

-ionizing radiations

2. Chemical sterilization

a. gaseous sterilization

(ethylene oxide, ozone , formaldehyde etc.)

b. Sterilization by heating with bactericide.

(chlorocresol-0.2%, phenyl mercuric acetate/ nitrate 0.002 %, Benzalkonium chloride- 0.01% etc)

3. mechanical processes of sterilization ;

removal of microbes by bacteria proof filter.

(ceramic filter, sintered glass filter, membrane filters)

Physical sterilization

This class includes heat sterilization and radiation sterilization .

Heat sterilization procedure is the one in which the destruction of microorganisms mainly occurs due to the high temperatures employed. This process includes

(a). Moist heat sterilization.

(b). Dry heat sterilization.

Dry heat sterilization

Mechanism :

The vital constituents of cells such as proteins (enzymes) and nucleic acids are denatured by oxidation.
it is a function of the time-temperature combination.
simplest and most economical method .

Types:-

- Flaming
- Hot air oven.

Hot air oven

- Double walled chamber of S. Steel/Al
- Insulation by glass fiber or asbestos
- Electric Fan(*Mechanical convection type)
- Temperature (160 ^{o}C for 2 hr)

Advantage

- For sterilization of those substances which get spoiled during moist heat sterilization, e.g. oily materials and powders.
- Suitable for sterilization of assembled equipments.
- Less damaging to glass and metal equipment.

Disadvantage

- Not suitable for surgical dressings.
- It requires very long heating up time, high temperature and long exposure time.
- Preparation containing water, alcohol or volatile substance can not be sterilize by this process.

Application

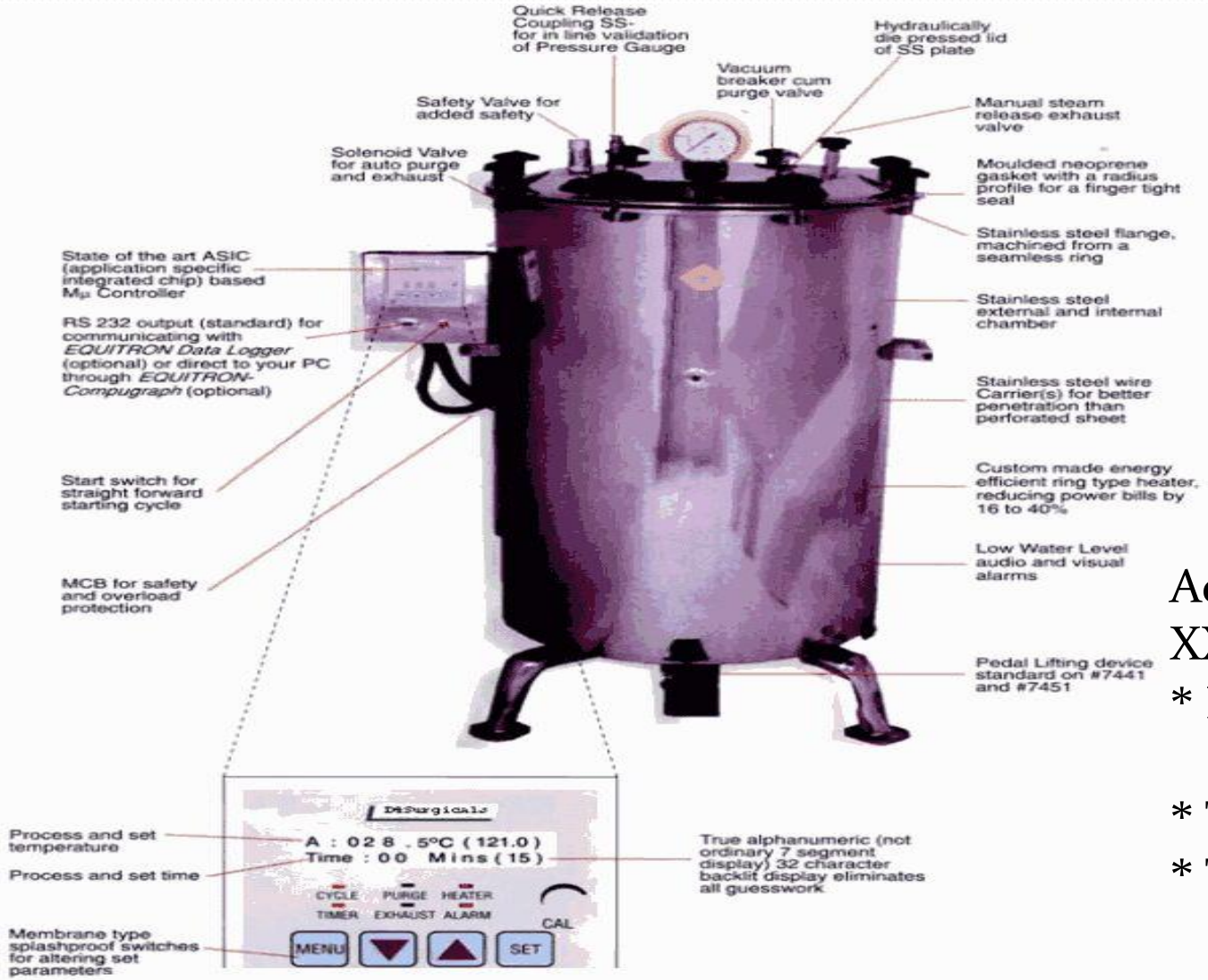
- For sterilization of glass wares, such as, pestle and mortar, flasks, bottles, test tubes etc.
- For sterilization of powders, such as, sulphacetamides, kaolin, talc, zinc oxide, starch etc.
- For sterilization of scalpels, scissors, spatula, blades, and glass syringes.
- For injections (fixed oil as vehicle): e.g. inj of progesterone, testosterone propionate etc).

Moist heat sterilization

Moist heat sterilization (steam sterilization under pressure).
Mechanism of killing of microorganisms: Denaturation and coagulation of essential protein molecules (enzymes) and cell constituents.

Moisture content (%)	Temp. required(°C)	Effect
50 25 0	56 80 170	Coagulation Coagulation Coagulation and oxidation

Autoclave



According to the USP XXI and BP 1988 are :

* Pressure:15 lbs / square inch (psi)
* Temperature: 121 ^{0}C
* Time: 15 minutes

Advantage

- Autoclaving destroys microorganisms more efficiently than dry heat and hence the Material is exposed to a lower temperature for a shorter period
- Sterilization of large number of official injections which h can withstand 15 psi for 30 minutes.
- A large quantity of material can be sterilised in one batch using a big autoclave
- A surgical dressing/ instruments, containers& closures

Disadvantage

- It is unsuitable for sterilisation of powders, oils, fats ointment etc.
- It can not be used for sterilisation of injections and articles, such as, plastics which get spoiled.

Radiation Sterilization

TYPES:-

1.Sterilization by U.V. light

2.Sterilization by ionizing radiation (X ray, gamma ray)

U-V Radiation

Drinking water UV sterilizer

Application

- Sterilization of air
- Thermolabile substances before packing (inactivation of virus & bacteria in vaccines)
- Maintenance of aseptic area
- Sterilization of surfaces of working tables and room
- In hospitals, UV radiation is used to control the spread of infection during or after surgical procedures

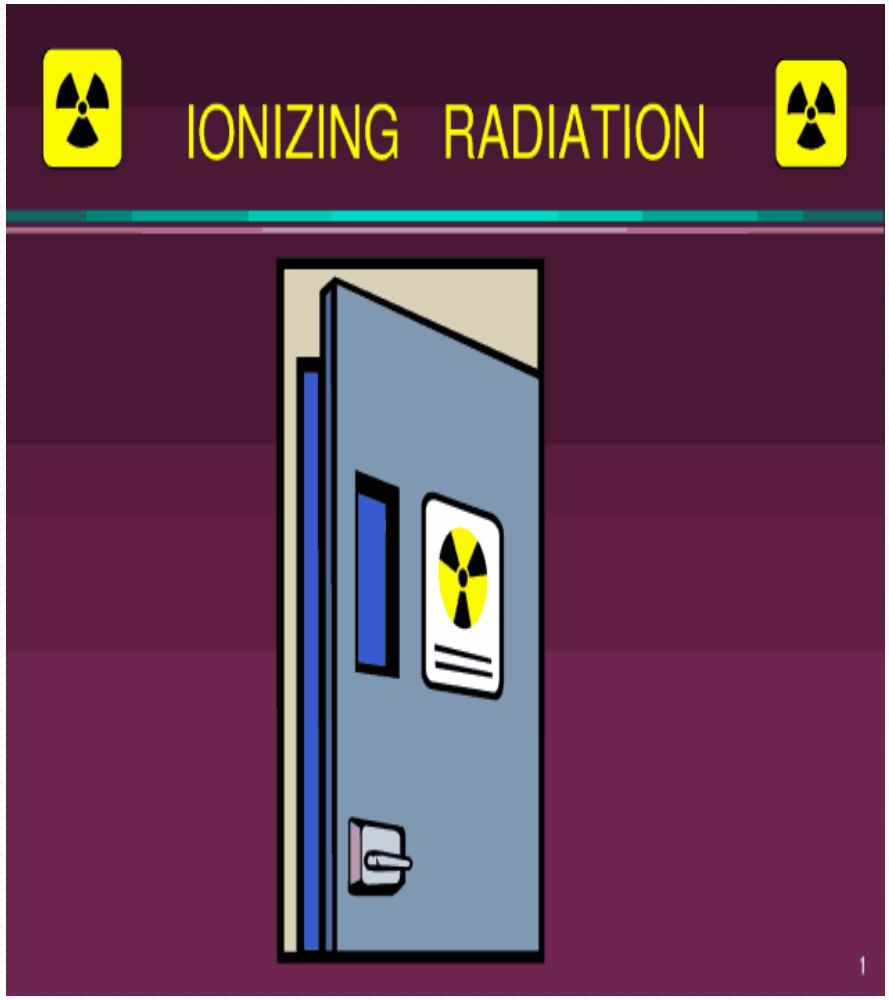
Disadvantage

- Low penetration power.
- Less effective, if the relative humidity is high.
- Harmful for worker.

Ionizing radiations

Gamma rays

Source : Cobalt-60
Mechanism: Mutation
1.Direct hit
2.Indirect hit



Advantage

- High penetration power
- No aseptic precautions are required
- Suitable for all types of materials
- Reliable
- Large quantity of material can be sterilized because the exposure time is very short
- Bacterial and viral vaccines (Influenza, Poliomyelitis and Rabies)
- Thermolabile drugs such as penicillin, streptomycin, thiamine, and riboflavin have been effectively sterilized by ionizing radiation.

Disadvantage

- Very costly
- Cannot be stopped
- Harmful to workers
- Undesirable changes in many medicaments

Application

- Sterilization of plastic syringes, needles, surgical blade etc.
- Sterilization of bone and tissue transplant, plastic tubing, catheters and sutures.
- Sterilization of thermolabile medicaments

Chemical sterilization

Types :-

A) Sterilization by heating with a bactericide
B) Gaseous sterilization

Sterilization by heating with a bactericide

Examples :- (chlorocresol-0.2%, phenyl mercuric acetate/ nitrate 0.002 %, Benzalkonium chloride-0.01% etc)

Application :-

- For aqueous preparation unstable at higher temperature

Disadvantage:

- Not for intrathecal injection
- I.V. injection > 15ml

Gaseous sterilization

Example:- Ethylene oxide(is a cyclic ether that has flammable and explosive so often used in combination with inert gases such as carbon dioxide)

Combination :- 1:9 (C_2H_4O:CO_2)

Mech:-Alkylation of protein molecules

Protein-NH_2 +C_2H_4O $\longrightarrow$ Protein-NH –(C_2H_4OH)

Protein-SH +C_2H_4O $\longrightarrow$ Protein-S –(C_2H_4OH)

Advantage

- It is suitable for heat sensitive substance (at room temperature)
- Very reactive compound, damage to only few material
- Very reliable (bactericidal)
- Good penetration power (pre packed article)
- For moist sensitive substance because low humidity is required
- No residual effect
- Effective against all organism

Disadvantage

- Very slow
- Expensive
- Highly toxic and inflammable
- Not for vitamins (Destroyed)
- Not for hypodermic needles, as gas can not penetrate

Application

- For thermolebile materials (Rubber and plastic items)
- For delicate instrument used in an OT
- Thermolabile powdered drugs such as Penicillin's
- Sterilization of powders, packed in plastic envelope which are permeable to gases
- Sterilization of instrument, metallic equipment, plastic syringes, disposable needles, tubing sets, dialysis units and needle.

Mechanical methods

Filtration sterilization:

- For sterilizing thermolabile solutions
- The drug solutions are passed through the sterile bacteria proof filter unit and subsequently transferring the product aseptically into the sterile containers which are then sealed
- Test for sterility of the filtered product

Advantage

- Suitable for thermolabile solutions
- Removes all kind of bacteria and fungi
- Filtration and sterilisation both simultaneously
- Convenient for large volume solutions
- Useful for eye drops, as dropper bottles can't withstand heating process

Disadvantage

- Requires trained staff
- Test of sterility
- Does not remove viruses, bacterial products (toxins and pyrogen)
- Sudden breakdown of membrane filter
- Adsorption in case of some filters
- Leakage in the filter unit may permit entry of not sterilize air
- If proper pre filtration has not done it may clog after prolonged filtration
- Not for suspension

THANK YOU