



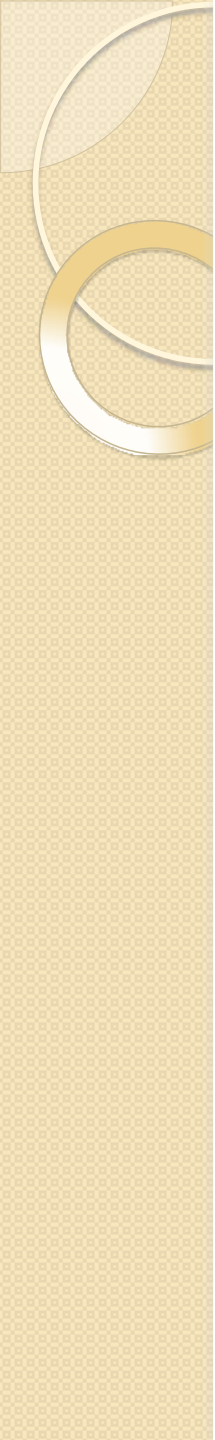
INDUSTRIAL
STERILIZATION ON LARGE
SCALE

**INDUSTRIAL
STERILIZATION ON LARGE
SCALE**

**Deepankar ratha
Assistant professor,
CUTM, Rayagada**

STERILIZATION

- Sterilization can be defined as the process through which all forms of life are destroyed, removed or permanently inactivated.
- Sterilization is essential concept at large scale as well as small scale for the preparation of sterile pharmaceutical products.

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- It's aim is to provide a product that is safe and eliminates the possibility of contamination.

WHY

- To reduce amount of contaminant's present in environment, on surface of container's, closure's as well as equipment's and to achieve better sterile condition.

SOURCE'S

- Raw materials
- Equipment & instrument's
- Manufacturing process
- Container & closure system
- Manufacturing environment
- Worker's

STERILIZATION PROCESSES

- The sterilization is done by
 1. Physical method
 2. Chemical method

Physical Method

- Moist heat
 1. saturated steam autoclave
 2. superheated water autoclave
 3. air over steam autoclave

- Dry heat
 1. continuous tunnel sterilizer
 2. hot air oven
 3. Red heat
 4. Flaming



- Radiation

1. Non-ionizing radiations

- Ultraviolet (UV) light

2. Ionizing radiations(cold sterilization)

- X-rays
- Gamma rays
- Cathode rays



- Filtration

1. Depth filter

- sintered glass filter

2. Screen filter

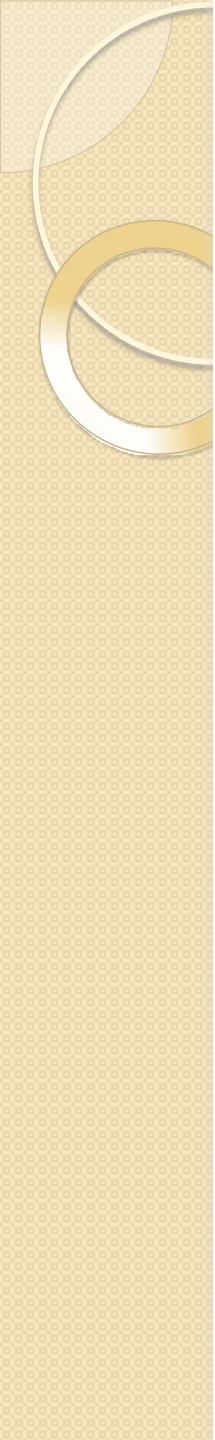
- particulate filter
- microbial filter

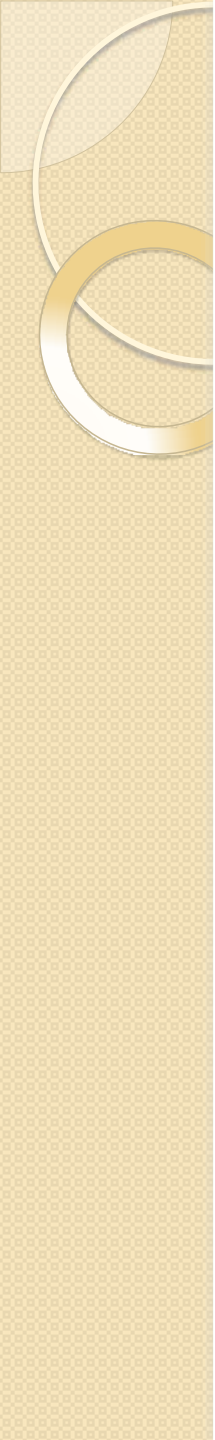
Chemical Method

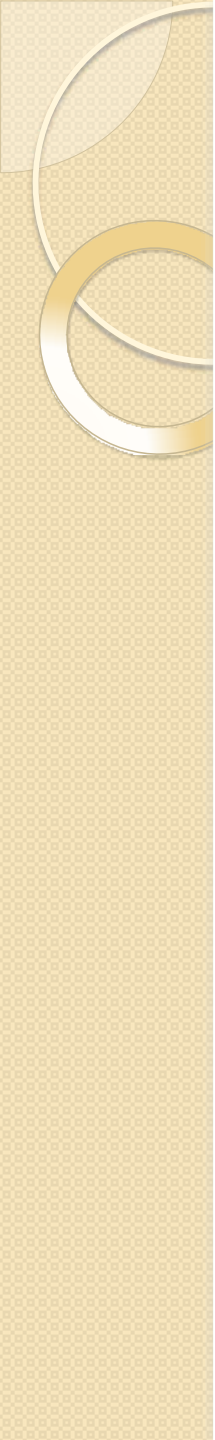
- Chemical sterilization
 - Gaseous sterilization
 - Ethylene oxide
 - Formaldehyde
 - By using disinfectant or antimicrobial agent

PROCESS SELECTION

- Process selection is most important and sensitive point for preparation of product.
- Those product intended to be sterile should be terminally sterilized in their final container as clearly stated in EUROPIAN PARMACOPOEIA.
- Where it is not possible to carry out terminal sterilization, choose the alternative method.

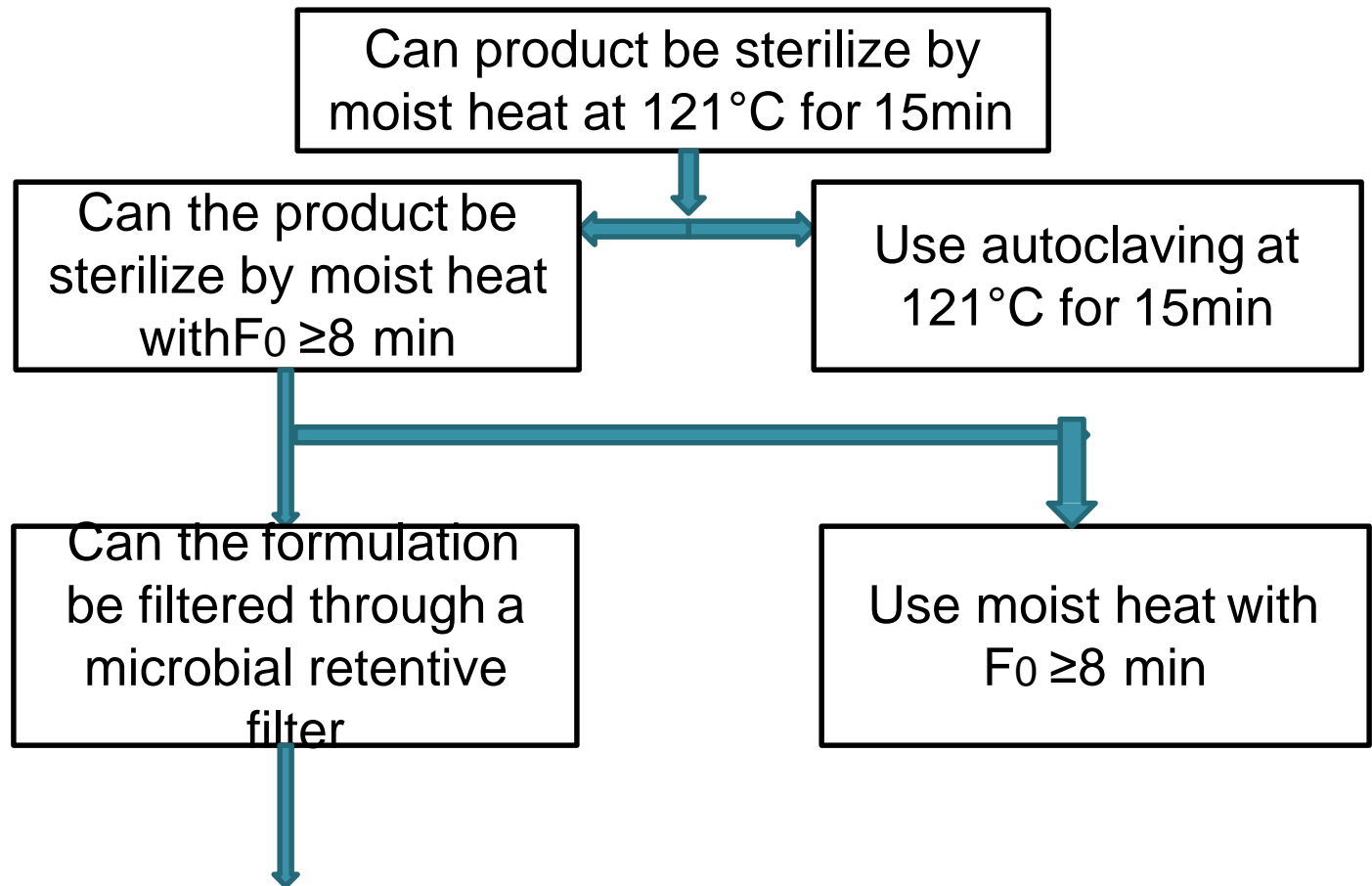
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- It is recognised that new terminal sterilization process other than those describe in p'copoeia may be developed to provide sterility assurance level equivalent to present official method, & such process when properly validated may offer alternative approaches.

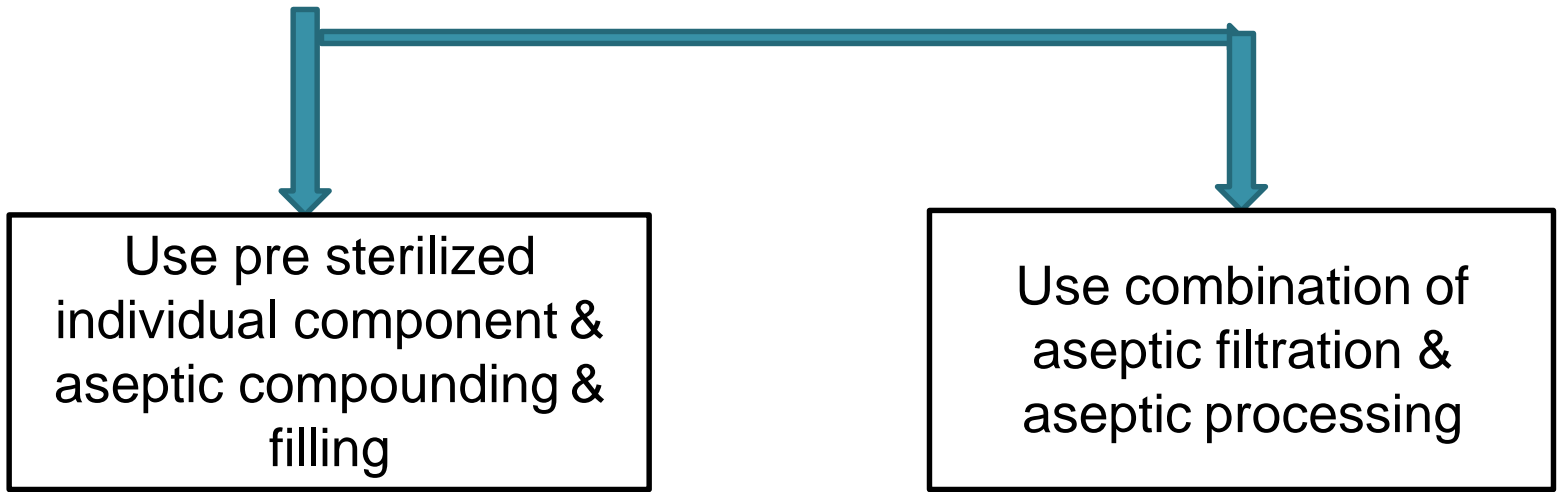
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- The use of an inappropriate heat labile packaging material can not in itself be the sole reason for adoption of aseptic processing, rather manufacturers should choose the best sterilization method achievable for a given formulation & select the packaging material accordingly.

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- The choice of packaging material for given product has to take into account factors other than the method of sterilization.
 - In such cases these other factor need to be clearly documented, explained & scientifically justified.

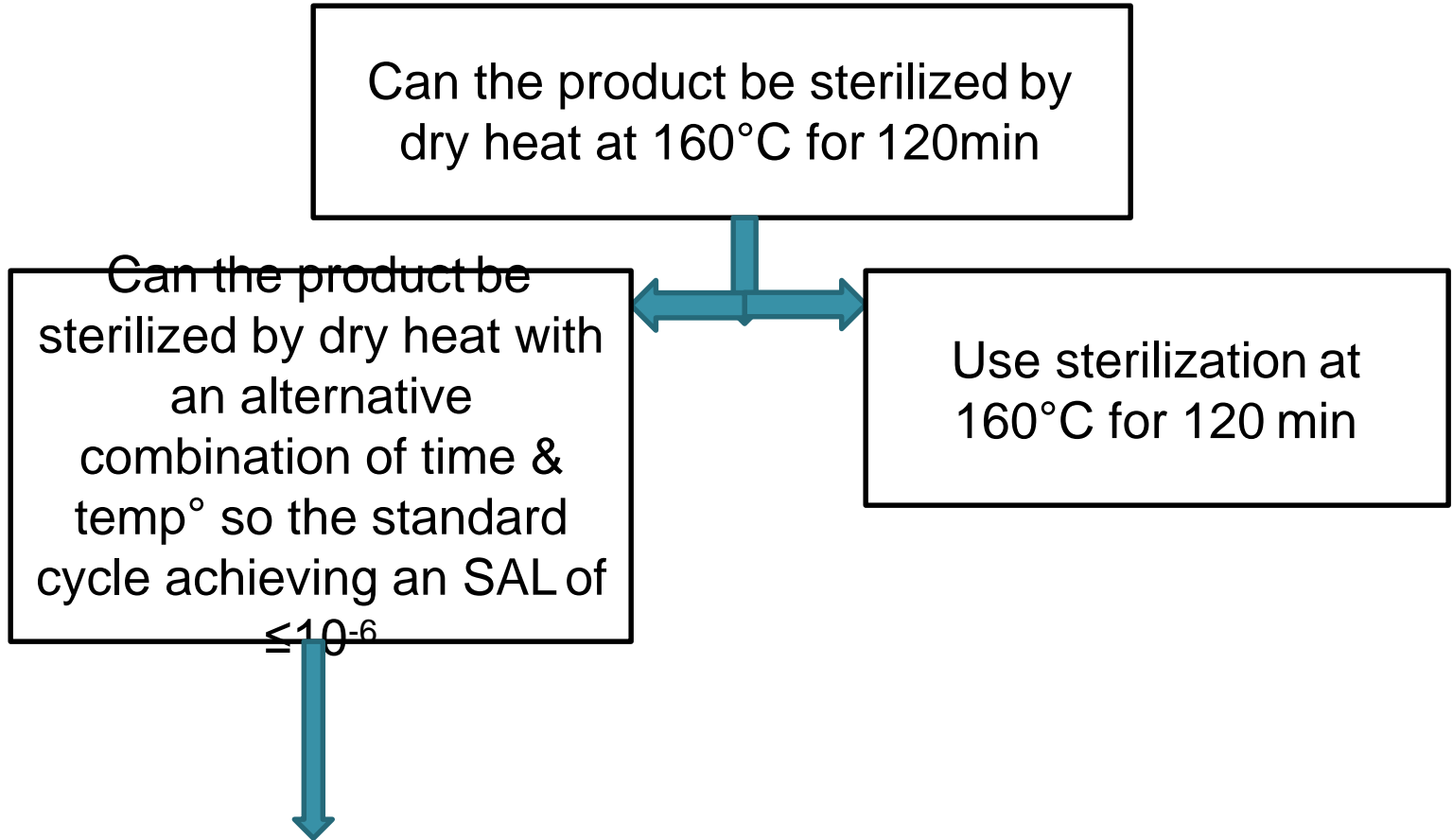
PROCESS FOR AQUEOUS PREPARATIONS

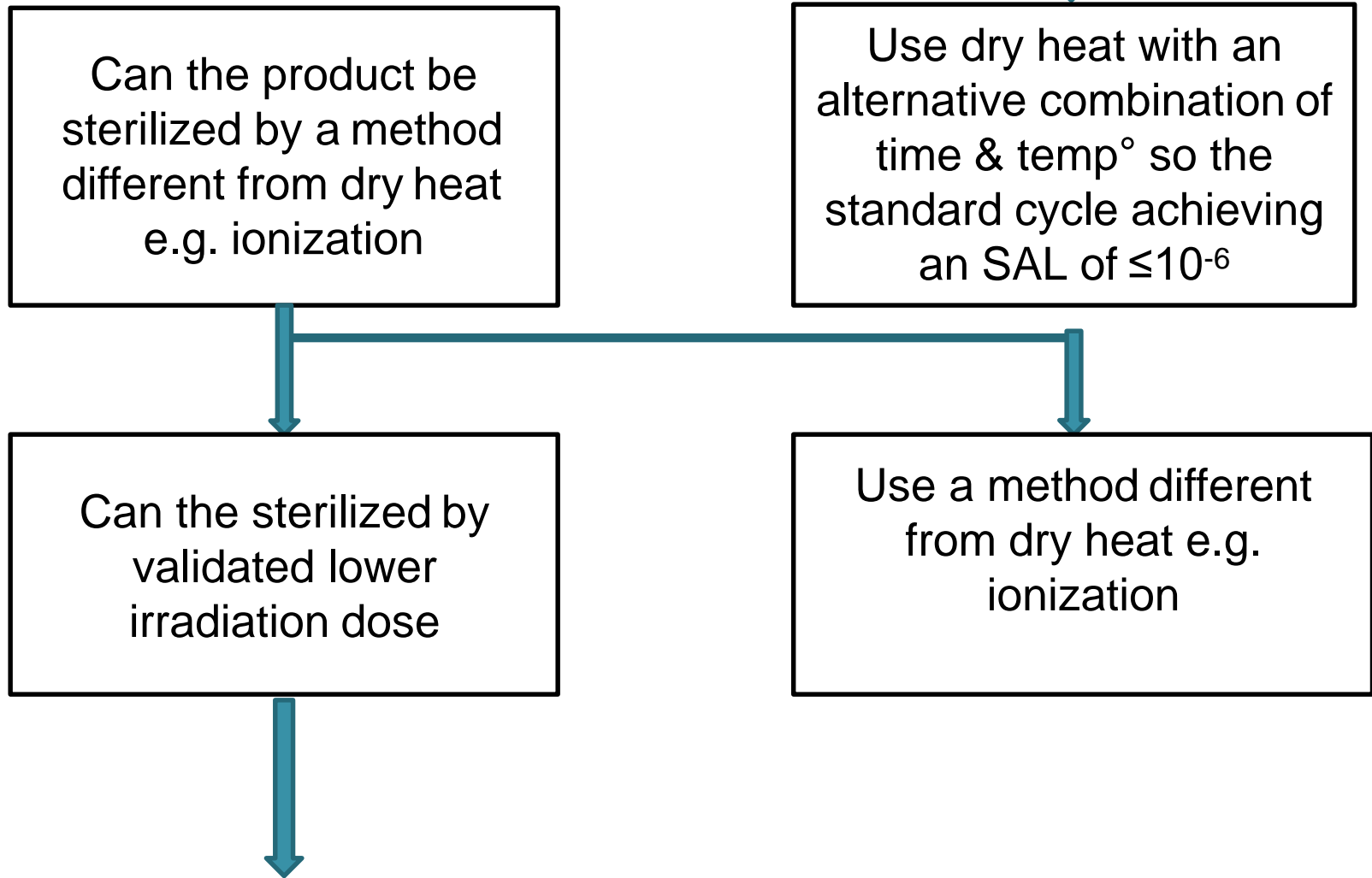
If the product is aqueous





If the product is non-aqueous, semi solid or dry powder





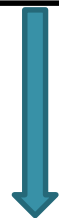
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graph TD; A[ ] --> B[Can the product be sterilized by a method different from dry heat e.g. ionization]; A --> C[Use dry heat with an alternative combination of time & temp° so the standard cycle achieving an SAL of ≤10-6]; B --> D[Can the sterilized by validated lower irradiation dose]; B --> E[Use a method different from dry heat e.g. ionization]; D --> F[ ]; style A fill:none,stroke:none; style F fill:none,stroke:none;
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Can the product be sterilized by a method different from dry heat e.g. ionization

Use dry heat with an alternative combination of time & temp° so the standard cycle achieving an SAL of $\leq 10^{-6}$

Can the sterilized by validated lower irradiation dose

Use a method different from dry heat e.g. ionization



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graph TD; A[ ] --> B[Can the formulation be filtered through a microbial retentive filter]; A --> C[Use the sterilized by validated lower irradiation dose]; B --> D[Use pre-sterilized individual components & aseptic compounding & filling]; B --> E[Use filtration & aseptic technique];
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Can the formulation be filtered through a microbial retentive filter

Use the sterilized by validated lower irradiation dose

Use pre-sterilized individual components & aseptic compounding & filling

Use filtration & aseptic technique

SPECIFICATIONS

- MOIST HEAT STERILIZATION
 - Micro organisms destroyed by cellular protein coagulation
 - The objects to be sterilized are exposed to saturated steam under 1 atmosphere pressure at a minimum temperature of 121°C for 15 min.
 - An autoclave is commonly used for moist heat sterilization.
 - Because it does not require as high a temp^o, moist heat sterilization cause less product and equipment damage compared to dry heat sterilization.

AUTOCLAVE

- Is a device to sterilize equipment and supplies by subjecting them to high pressure saturated steam at

Temp°C	lb/sq.inch	Time(min)
115-118	10	30
121-124	15	15
126-129	20	10
135-138	30	3

TYPES

- Portable autoclave (Bench autoclave)
- Stationary autoclave (Large sterilizer)





- Main Features

- Lid(door) fitted with clamps and asbestos jacket , stationary autoclave may be double doors at both ends one for loading and one for unloading.
- Pressure gauge
- Thermocouple for measurement of temp^o.
- Air vent to remove air before sterilization.
- Safety valve to permit escape of excess steam to prevent explosion .
- Modern autoclaves are recording (record pressure, temp during the whole process) supplied with timer and are automatically controlled .



- DRY HEAT STERILIZATION

- Is appropriate for materials that cannot withstand moist –heat sterilization (e.g., oily materials and powders)
- Objects are subjected to a temperature of at least 160° for 120 minutes(if higher temperatures can be used , less exposure time is required)

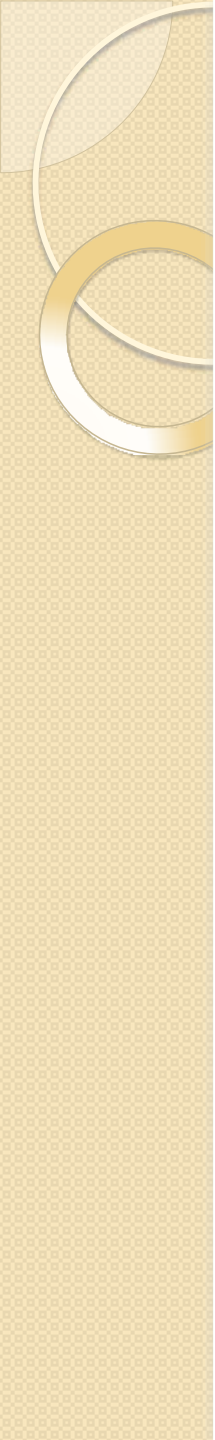
HOT AIR OVEN

- Is a device to sterilize subject and supplies by subjecting them to direct heat at

Temp°C	Time(min)
170	60
160	120
150	150
140	180

- Is appropriate for the materials that can not withstand steam sterilization (e.g. oily materials & powders)
- If higher temperature can be used, less exposure time is required.

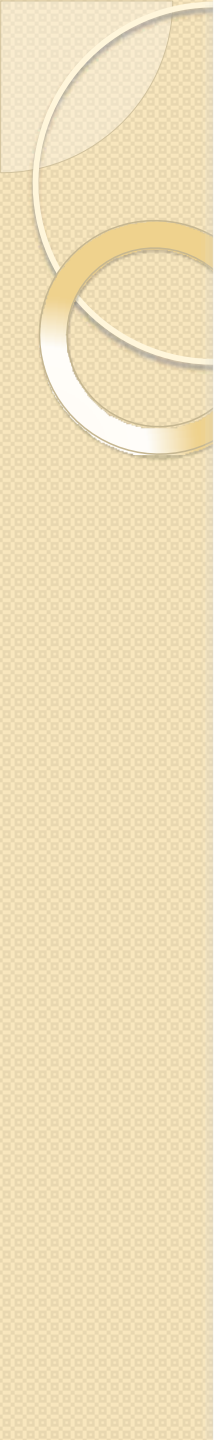


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- Main Features
 - Door fitted with the clamps and asbestos jacket has the single door
 - Regulator for temperature control
 - Fan attached inside for air circulation
 - Perforated shelf for keeping subject inside

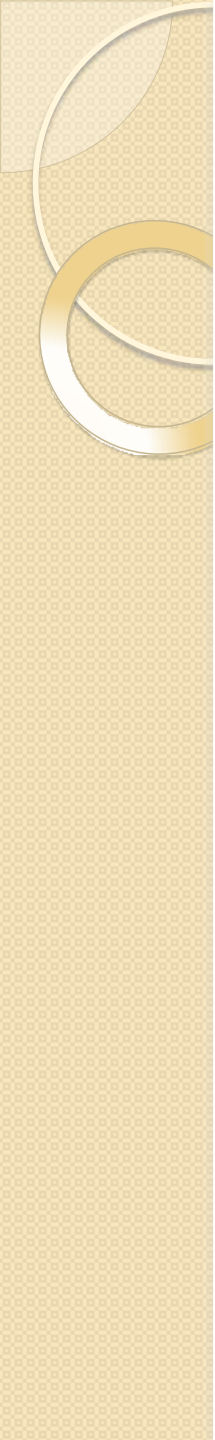


- RADIATIONS

- Energy transmitted through space in variety of forms is generally called radiation
- This method is also called as cold sterilization because it produce relatively little heat
- Thus, it is possible to sterilize heat sensitive materials such techniques are being in food industries mainly

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- Non ionizing radiations (UV)
 - UV in region of 2537 Å has been shown to possess the greatest activity in destroying MO
 - Commonly employed in reduction of airborne contamination in the maintenance of aseptic areas & rooms
 - Source of artificial UV radiations is UV lamps (generally called sterilizing lamp or germicidal lamp)
 - UV light is absorbed by the nucleic acid of the cell where it does the greatest damage

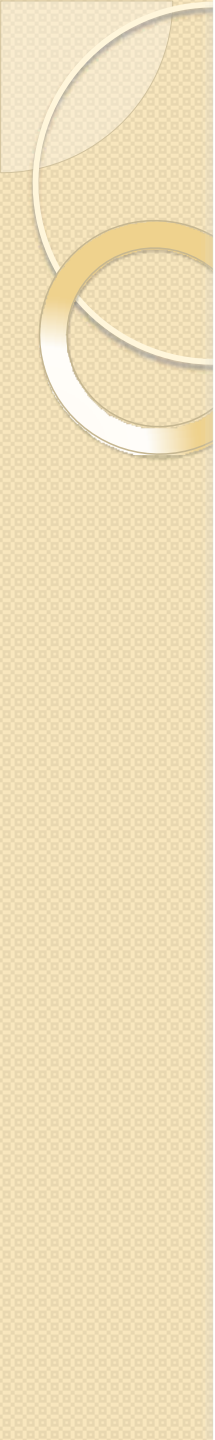


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- Ionizing radiations (cold sterilization)
 - X-rays, gamma rays & cathode rays are lethal to DNA & other vital cell constituents
 - They have high penetration power & considerable energy
 - The factors that effect the lethal activity of ionizing radiations are oxygen effect, protective compounds, sensitizing agents, pH of cultures, freezing, moisture & recovery conditions



- Filtration

- This is a non-thermal method of sterilization used widely in the pharmaceutical industry where heat labile solutions are to be sterilized
- This is useful for large volume solutions, eye drops, antibiotic solutions, sera & carbohydrate solutions
- This also useful for separation of bacteriophages & bacterial toxins from bacteria for the isolation of MO which are scanty in fluids

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- 3 main stages involved in filtration
 1. Passage of the solution through a previously sterilized bacteria-proof filter unite
 2. Aseptic transference of filtrate to sterile containers then sealed aseptically
 3. Testing of sample for sterility



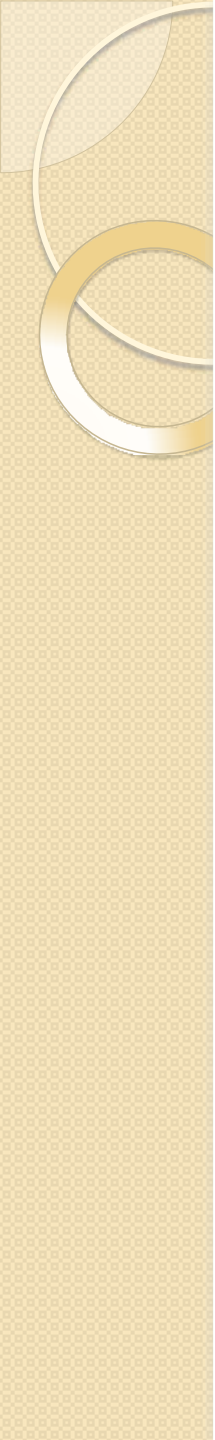
- Gaseous sterilization

- The destruction of all living MO with chemical in gaseous or vapours state
- When material is affected by the dry or moist heat then the gaseous sterilization is used
- All these gases are toxic to human being above certain conc. and may exhibit other undesirable side effect
- Ethylene oxide is most widely used gaseous sterilization agent in pharmaceutical industry
- In addition to these, various glycols, methyl bromide and alcohol have been used for room sterilization

- Ethylene oxide

- It is colorless liq. with BP 10.8°C
- Highly inflammable and may be explosive when mixed with air in conc. Greater than 3%. Its mixture with CO₂ in certain proportion makes it inflammable
- Conc. & time relationship commonly for sterilization is as below

	conc.(mg/lit)	exposure
ti	e(hrs.)	
	44	24
	88	10
	442	4
	884	2

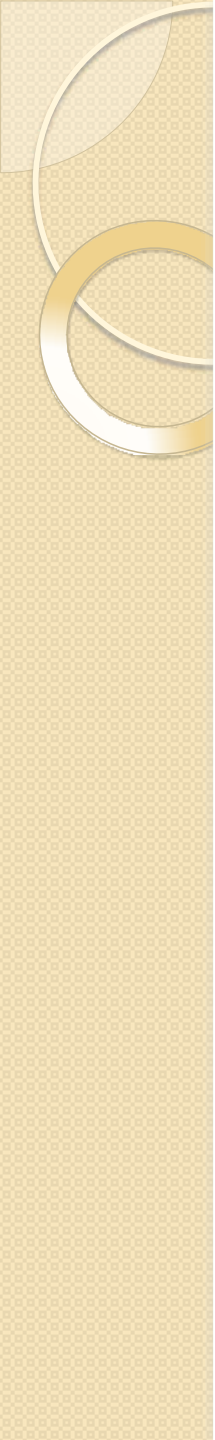
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- Disinfectant or antimicrobial agents
 - Chemical agents most commonly used as disinfectant and antiseptic e.g. phenols, alcohols, halogens, dyes, aldehyde etc.



DEVELOPMENT & VALIDATION OF PROCESS & EQUIPMENT

Process validation:

- It is analysis of data gathered throughout the design & manufacturing of product in order to confirm that the process can reliably output products of determined standard.
- Regulatory authorities like EMA & FDA have published guidelines relating to process validation

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- The purpose of validation is to ensure varied inputs lead to consistent & high quality outputs
 - Process validation is an ongoing process that must be frequently adapted as manufacturing feedback is gathered
 - End to end validation & production is essential in determining product quality because quality can not always be determined by finished product inspection

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- Process validation can be broken in to 3 steps

1. Process design
2. Process qualification
3. Continued process verification

- Process design:

In this data from the development phase are gathered & analyzed to define the commercial manufacturing process. The data used to establish benchmark for quality & production control



- Process qualification:

In this stage the process design is assessed to conclude if the process is able to meet determine manufacturing target. All the process & manufacturing equipment is proofed to confirm quality & output capabilities

- Continued process validation:

It is the ongoing monitoring of all aspects of production cycle. It aims to ensure that all levels production are controlled & regulated



EQUIPMENT VALIDATION/ QUALIFICATION

- Equipment validation is divided into
 1. Design qualification
 2. Installation qualification
 3. Operational qualification
 4. Performance qualification



- DQ:

It define the functional & operational specification of the instrument & details for the continues design in selection of supplier

- IQ:

Demonstrates that the process or equipment meets all specifications, is installed correctly, and all required components and documentation needed for continued operation are installed and in place.



- OQ:

Demonstrates that all facets of the process or equipment are operating correctly.

- PQ:

It is the process of demonstrating that an instrument consistently performed according to specification appropriate for it's routine work