

UNIT-V

Sources and types of microbial contaminants



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Introduction

- Spoilage is **chemical and physicochemical degradation of pharmaceutical products** rendering it **unsuitable for use**.
- Spoilage is not desirable in pharmaceutical industry because deterioration of drugs and excipient occurs, as a result **product may lose its quality and it may become ineffective**. Entire batch may be required to be discarded.
- This **may cost huge loss** to the manufacturer. Moreover it **may attract litigation** from the consumers which **may cause huge financial loss** to the Company.

Source and types of microbial contaminants

- Microbes are very important part of our environment. They are present almost anywhere and everywhere. So, contamination may occur to pharmaceutical products **in large scale manufacturing**, in small scale hospital manufacturing or during use by the patient.
- Following are the different source of microbial contamination in pharmaceutical products.
- **In large scale manufacturing:** - In large scale manufacturing as well as **medium and small scale** manufacturing contamination may occur from following sources.

Water

- Water is a major source of contamination. Common water borne micro-organism like *Pseudomonas*, *Achromo* bacteria and other **low demand gram negative groups** are present in **portable water as well as in purified water.**
- **Ion-exchange column** may be contaminated by water source and micro-organism may multiply there to contaminate purified water.
- Water which is purified by **reverser osmosis process** may also be contaminated if osmosis membrane is no properly disinfected.
- Even **distilled water may also be contaminated** if it is stored for few day at normal temperature.

Raw materials

- Pharmaceutical products are prepared from varieties of raw materials. **Clays** and **earth materials** like **bentonite**, **kaolin** etc may contain **anaerobia spores** like *Clostridium sp.*
- **Starch** may contain **coliform** bacteria like *E. Coli*. **Gums** may contain *Actinomyces*.
- **Animal products** may contain a variety of bacterial like *E. coli*, *Salmonella species* etc.

Human source

- Pharmaceutical products may be contaminated during use. Patient **may self contaminate** his medicine. Contaminants **may travel to other patients through doctors nurses** etc.

Air of the manufacturing area:

- Air is filled with billions of suspending particles and microbes. **Fungus spores**, like **penicillium, mucor, Aspergillus** etc. Bacterial spores like ***Bacillus* sp.** etc are also present. These spores and micro-organism may contaminate pharmaceutical products. This type of **contamination is minimized by practice of manufacturing in clean room and in aseptic room under continuous flow of sterile air through HEPA filter.**

Personnel:

- Manufacturing staff may also contaminate pharmaceutical products. Personnel may be infected with various types of infections like **coliform bacteria, staphylococci, streptococci, Actino bacteria, Candida.** This types of contamination may be minimized by proper health **check-up, vaccination and hygiene of the personnel.** Protective gear and proper training of the personnel may also minimize the contamination.

Equipments

- Equipments of manufacturing may contain microbes if it is not sterilized properly. Grinder, blender, filter etc may contain non-specific and local communities of micro-organism.

Containers:

- Containers may cause contamination if it is not sterile.
- **In hospital manufacturing** -In hospital manufacturing water and environment are the major source of contaminants. In hospitals, water is stored in storage tank which may develop fungus, bacteria and algae type of microbes. Hospital air may be contaminated with pathogenic microorganism **due to the presences of infected patients** and numerous visitors.

Preservation of pharmaceutical products using antimicrobial agents:

- Antimicrobial agents are those substances which can kill or inhibit growth of micro-organism.
- These antimicrobial agents are included in formulation in order to minimize levels of contaminated micro-organism. These **antimicrobial agents are called preservatives.**
- These preservatives can generally **prevent or kill low levels of contamination.** Preservatives are not used in those formulations which has low risk of contamination and subsequent microbial growth.
- Formulations which contains **high level of acid, alkali, sugar** etc may **not require** preservative. Formulations of antibiotics and other anti-microbial substances may not require preservative.

- A good preservative should have following characteristics. It should be a broad spectrum antimicrobial agent, *i.e.* **it should be effective against variety of microorganisms.** However, most active **preservatives are ineffective** against some microbes.
- A good preservative should have a **fast killing and inhibition rate** and it should **selectively react with contaminants** and it **should not react with ingredients of the formulation.**

- However, most preservatives interact with ingredients of the formulations. A good preservative **should be non-irritant and non-toxic to the patients**. However, many preservative **have toxic effects** and cause **irritation of skin** when used in formulation for topical application.
- Some preservatives even cause **contact dermatitis**. A good preservative **should be stable** and it should **remain active throughout the shelf-life** of the product. However effectiveness of the preservative may change depending upon so many factors.

- **Concentration of preservatives determine efficacy of its preservation power.** Antimicrobial activity of preservative increases with the concentration. Activity of phenol decreases 64 times if concentration is turned in to half.
- Antimicrobial activity of preservative is also **dependent on storage temperature.** Decrease in storage temperature may **reduce killing activity** of preservative. It may be calculated by **determining temperature co-efficient.**
- Preservative which is used in formulation may not be available for antimicrobial activity. An unstable equilibrium is formed between preservative and available preservative which controls mass of micro-organism. Unavailable preservative helps to maintain equilibrium by constantly supplying available molecule.

- **Availability of preservative** may also **decrease** with **increased solute concentration** and **decrease water activity**. **Ionic and weakly acidic preservatives** exhibit their **antimicrobial activity** when they are **not ionized**. They produce **maximum** activity when **ionization is very low**.
- Preservative may **distribute itself depending its affinity** in a **multiphase** system. It may distribute itself in **water phase and oil phase by an unstable equilibrium**. Parameters like **partition coefficient, polymer binding constant and oil-water ratio** must be considered while using a preservative in a formulation.
- **Packaging material** can interfere with preservation activity of preservative. Preservative may **leach, permeate** and interact with **rubber, plastic, cork** etc.

- Different types of preservatives are used in pharmaceutical products. Acid, alkali and esters are used as preservative. **Benzoic acid** is used as preservative. Its **sodium salt, sodium benzoate** is also used as preservative. Its ester methyl **hydroxybenzoate** is also used as preservative.
- Some alcohols like **chlorobutol**, benzyl alcohol etc are used as preservative. Some **phenolic compounds** like **phenol, chlorocresol** etc are also used as preservatives.
- Some **mercuric compounds**, such as **thiomersal** etc are used as preservative. Many other compounds like **benzalkonium chloride, cetrimide** are used as preservative. Even compounds like **chloroform and formaldehyde** can be used as preservative.