

UNIT-V

Preservation of pharmaceutical products



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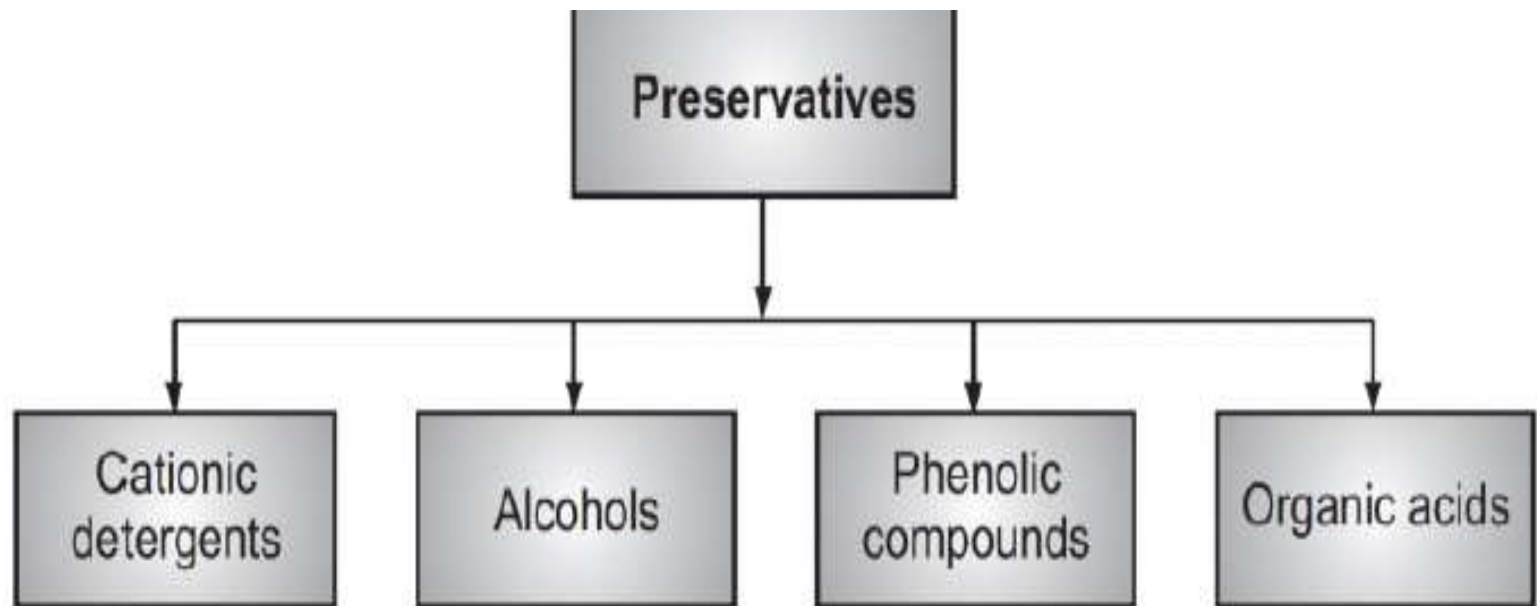
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- A preservative is an antimicrobial substance added in the pharmaceutical formulations with the view to avoid contamination in the formulation.

Ideal Properties of Preservatives:

- Should not cause irritation.
- Should be non toxic and stable.
- Should be effective during shelf life of the formulation.
- Should kill all contaminants effectively and rapidly.
- Should not react with ingredients of the formulation.
- Should not interact with the container and closure system of the dosage form.

- The main purpose of these preservatives is to inhibit growth of microbes in the pharmaceutical product. They can be classified into four major groups as,
 - Acidic,
 - Mercuric,
 - Neutral,
 - Quaternary Ammonium Compounds.



Flowchart 1: Types of preservatives

1. Cationic detergents: Examples: Benzalkonium chloride, alkyl trimethyl ammonium chloride.
2. Alcohols: Examples: Chlorbutanol, bronopol, phenyl, and phenoxyethanol.
3. Phenolic compounds: Examples: chlorinated and isopropyl derivatives of meta cresol.
4. Organic acids: Examples: Salicylic acid, benzoic acid, acetic acid, lactic acid, hydroxyl benzoic acid.

Preservation of Pharmaceutical Products using Antimicrobial Agents

- Pharmaceutical products are substances or mixtures intended for use in humans for diagnosing, treating, or preventing disease.
- Pharmaceutical products are substances or mixtures intended for use in humans for diagnosing, treating, or preventing disease, altering or modifying bodily functions, or preventing abnormal physical states.
- Known as microbial spoilage, this occurs when these pharmaceutical products deteriorate as a result of contamination by microbes.
- Due to this, products must be preserved during storage and multi-dose use in order to reduce or eliminate spoilage caused by microbial contamination.

- Acyclovir, amantadine, flumadine (essential medicines) are examples of prescription drugs in the pharmaceutical industry, while biological products include vaccines, antibodies, blood, therapeutic proteins, tissues, and many more.
- Pharmaceutical products include needles, syringes, gloves, aspirin and paracetamol, which are OTC drugs.
- The products can contain microbes like *E. coli*, *Clostridium botulinum*, *Clostridium perfringens*, *Pseudomonas aeruginosa* and *Salmonella caveman*.

- As exceptions to a categorization such as this, antimicrobial preservatives help enhance antimicrobial stability and thus contribute to antimicrobial effectiveness. Consequently, the use of preservatives in pharmaceutical products containing antimicrobial agents is crucial. A good preservative should have the following properties:
 - Toxic or irritating effects should not occur at the specified concentration.
 - Microorganisms should not be able to grow under them.
 - Solubility in water is crucial so that the required concentration can be obtained.
 - Their heat stability should extend their storage capabilities.
 - Their chemical compatibility should extend across all formulations.
 - Containers and closures of the products should not adversely affect them.
 - The products should be inexpensive.

- The protection provided by preservatives against viral contamination is limited. Microbes and fungicides can affect a wide variety of cellular targets, including their cell walls, cytoplasm, and membranes. The target doesn't always remain the same for every preservative class; it changes with the concentration of preservatives. The preservatives should consist of:
 - Antimicrobial activity ranging from low inclusion levels to a wide spectrum.
 - Ability to remain active during manufacture, storage, and usage.
 - The quality of the product, the packaging, and the delivery system is never compromised.
 - Effect on the product's tolerance or safety.

Based on their mechanism of action, preservatives are classified as follows:

- 1. Antioxidants :** As active pharmaceutical ingredients are sensitive to oxygen, antioxidants prevent them from oxidizing.
- 2. Antimicrobial agents:** Micro-organisms that cause degradation of pharmaceutical preparations such as gram-positive and gram-negative bacteria can be neutralized by antimicrobial agents. These are active in a low-inclusion level. Ex: **Sorbate, Benzoate, Sodium benzoate**
- 3. Chelating agents:** Chemical agents are those capable of forming complexes with pharmaceutical ingredients and preventing degradation of the pharmaceutical formulation. Examples: **EDTA, polyphosphates, and citric acid.**

- Preservative systems protect products against the growth of microorganisms with these concepts.
- An antimicrobial agent's mode of action as a preservative: Inhibition of cell wall synthesis, protein synthesis, and DNA and RNA synthesis is how antimicrobial agents work.
- **Sorbates, propionates, nitrates and benzoates**, for example. Microbial growth will be supported by emulsions, which contain water.
- Emulsifying agents can be affected by microorganisms, which produce an unpleasant odor, color changes, and gases.

- To minimize the chance of spoilage, an antimicrobial "preservative" is added to multi-dose containers when they are stored or used repeatedly. Antimicrobial agents with strong activity are often not selective in action and interact significantly with all of the formulation ingredients as well as with patients and microbes.

Methods of Preservation

1. Physical protection: It is used for proper packaging of the pharmaceutical products under aseptic conditions or else there is a chance for microbial growth. Operating persons are also an important factor for the proper processing of the products under an aseptic environment.

2. Waterproof protection: The packaging of pharmaceutical products should be under waterproof protection because water favors the growth of microorganisms.

3. Preservative coating:

- Aqueous raw materials used in the formulation of paints and coatings create the perfect environment for the growth of bacteria, fungi, and yeast.
- They can destroy valuable pharmaceutical formulations. Controlling these microorganisms helps increase efficiency, helps deliver a better end-user product, and helps employees and consumers avoid contact with spoilage microorganisms.
- Biocides are necessary for protecting the integrity and functionality of water-based paints and coatings from destruction by microbial contamination as a result of lengthening of product's shelf life and protecting the dry film from algae, mold.

4. Water vapor proof protection: This method is applicable for certain pharmaceutical products when they are packing under proper care for minimizing microbial activity. For 'dry' dosage forms with a very low water activity protect against microbial attack. The moisture vapor properties of packaging materials require careful examination.

5. Water vapor proof protection with desiccant: This method is also used for dry products that absorbed moisture from the environment and are spoiled due to the growth of microorganisms. Packing should be proper with this method to minimize the microbial growth and spoilage of the products.

Factor affecting the efficacy and availability of preservatives:

- Temperature.
- Chemical structure of preservatives.
- The capacity of preservatives.
- Inoculum size.
- Effect of pH.
- Effect of containers and packaging.
- Changes of concentration.

Modes of Action of Preservatives

- Preservatives provide limited protection against viral contamination.
- Bactericides and fungicides may evince their effects on a variety of microbial cellular targets, for example; the cell wall, the cytoplasmic membrane, or the cytoplasm. It is sometimes difficult to assign a precise target for a specific class of preservatives; the target does change with preservative concentration.

Hence, they should have:

- A wide spectrum of antimicrobial activity at low inclusion levels.
- Maintain activity throughout product manufacture, shelf life, and usage.
- No compromise on the quality or performance of product, pack, or delivery system.
- Adverse influence on patient safety or tolerance of the product.
- With these concepts, the preservative system protects the product against microbial proliferation.

Mode of action of antimicrobial agents as preservatives:

- Antimicrobial agents act by cell wall inhibition, protein synthesis inhibition, DNA and RNA synthesis inhibition.
- For example Benzoates, Sodium benzoate, Sorbates, Propionates, Nitrites.
- Emulsions contain water which will support microbial growth. Microbes produce an unpleasant odor, color changes, and gases and may affect the emulsifying agents.
- Other ingredients of emulsions support the growth medium for microbes.
- Examples: Arachis oil supports *Aspergillus* species and liquid paraffin supports *Penicillium* species.

- Antimicrobial preservatives are added to non-sterile dosage forms to protect from microbiological growth or from microorganisms that are introduced inadvertently during or after the manufacturing process.
- In the case of sterile articles packed in multiple-dose containers, antimicrobial preservatives are added to inhibit the growth of microorganisms that may be introduced from repeatedly withdrawing individual doses.
- Examples of antimicrobial preservatives include alcohol, formaldehyde, and iodine.

- An antimicrobial ‘preservative’ is included in a formulation to minimize the risk of spoilage and to kill low levels of contaminants introduced during storage or repeated use of a multi-dose container.
- The strong antimicrobial agents are often non-selective in action but interact significantly with formulation ingredients as well as with patients and [micro organisms](#).