

Preservatives

Introduction to Alicyclic compounds

Definition and Importance

- A preservative is a chemical substance added to pharmaceutical formulations to prevent or retard microbial growth (bacteria, fungi, molds, and yeasts), and/or to prevent chemical degradation of the product.
- Preservatives do not have therapeutic effects, but they preserve the integrity, safety, and potency of formulations—particularly multi-dose products, which are exposed to microbial contamination each time they are used.

Necessity of Preservatives

- Preservatives are essential in:
 - **Multi-dose containers** (e.g., eye drops, syrups, injections).
 - **Aqueous-based formulations**, which are prone to microbial growth.
 - **Topical products** (creams, lotions), which are frequently exposed to the environment.
 - **Oral liquid preparations**, which may be stored over long periods.

Mechanism of Action of Antimicrobial Preservatives

Antimicrobial preservatives act through several mechanisms:

1. Cell wall lysis or membrane disruption:

- E.g., Benzalkonium chloride integrates into the cell membrane, causing leakage of cellular content.

2. Protein denaturation:

- E.g., Alcohols and phenols disrupt protein structures and enzyme systems.

3. Inhibition of metabolic enzymes:

- E.g., Sorbic acid inhibits microbial dehydrogenases.

4. Interference with nucleic acids:

- E.g., Formaldehyde crosslinks DNA and proteins.

Factors Affecting Efficacy of Preservatives

1. pH of the Formulation:

- Many preservatives are only active within a specific pH range.
- E.g., Benzoic acid is most effective below pH 5.

2. Concentration of the Preservative:

- Must be optimized: too low = ineffective; too high = toxicity or incompatibility.

3. Type of Microorganisms:

- Gram-negative bacteria are generally more resistant than Gram-positive.

4. Presence of Other Ingredients:

- Surfactants and other excipients may interact with preservatives and reduce their activity.

5. Packaging and Storage Conditions:

- Light, temperature, and container material can influence preservative stability and activity.

Application in Pharmaceutical Formulations

1. Ophthalmic Preparations:

- **Benzalkonium chloride** is widely used in eye drops.
- Must be isotonic, sterile, and non-irritating.

2. Injectable Products:

- Often contain **phenol**, **benzyl alcohol**, or **chlorobutanol**.
- Used only when absolutely necessary due to potential toxicity.

3. Oral Liquids:

- Use **parabens**, **sodium benzoate**, or **sorbates**.
- Must ensure taste is acceptable and compatible with other ingredients.

4. Topical Preparations:

- Use **methylparaben**, **propylparaben**, **phenoxyethanol**, or **benzyl alcohol**.
- Should not cause skin irritation or allergic reactions.

Ideal Properties of a Preservative

- Broad-spectrum antimicrobial activity.
- Chemically and physically stable over shelf-life.
- Compatible with APIs and excipients.
- Non-toxic and non-irritating at effective concentrations.
- Odorless, tasteless (or acceptable flavor profile).
- Soluble in the formulation.
- Should not adsorb to container or closure systems.

Preservative Efficacy Testing (PET)

- Pharmaceutical formulations containing preservatives are subjected to **Preservative Efficacy Testing**, also known as **Antimicrobial Effectiveness Testing (AET)**.

Procedure (as per pharmacopeias like USP/Ph. Eur):

1. The formulation is inoculated with standard strains of microbes.
2. At specific time intervals (6h, 7 days, 14 days, 28 days), microbial counts are taken.
3. The reduction in microbial count is evaluated to determine preservative effectiveness.

Common test organisms:

- *Staphylococcus aureus* (Gram +ve)
- *Escherichia coli* (Gram –ve)
- *Pseudomonas aeruginosa*
- *Candida albicans* (yeast)
- *Aspergillus niger* (mold)

Regulatory Guidelines

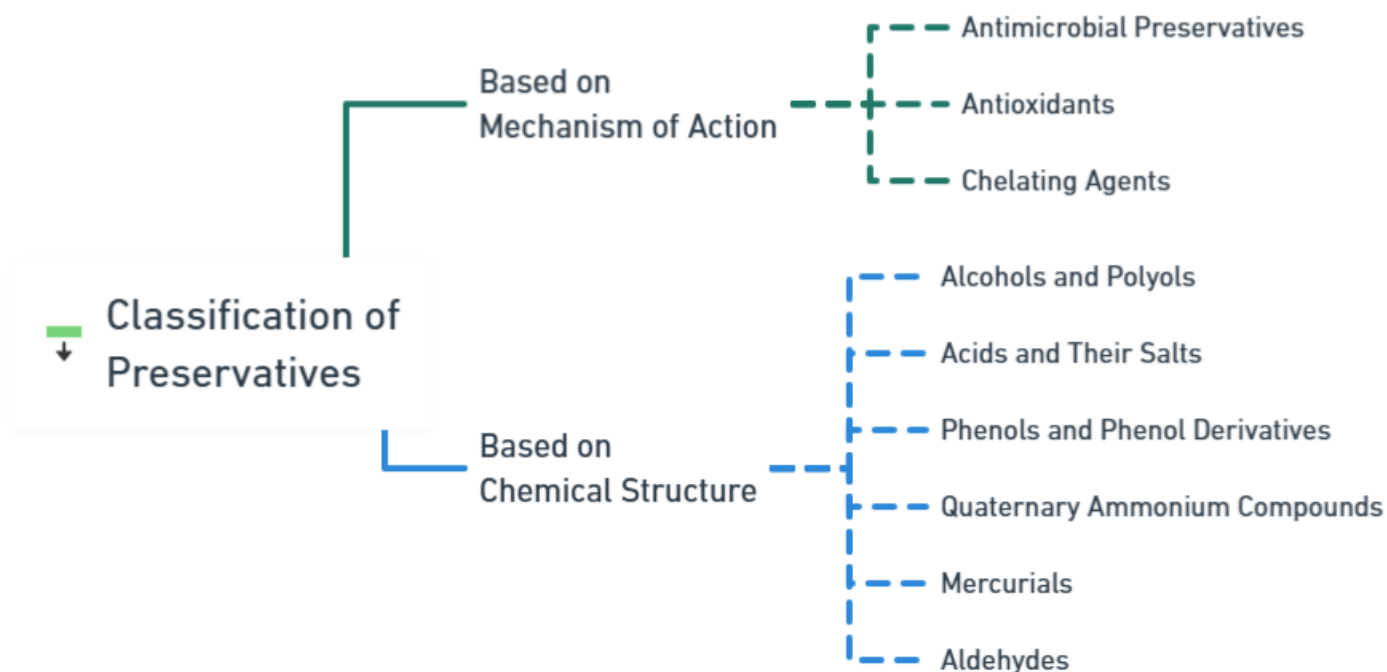
- Pharmaceutical preservatives must be used according to limits set by regulatory bodies like:
 - **USP (United States Pharmacopeia)**
 - **Ph. Eur (European Pharmacopoeia)**
 - **ICH Guidelines**
 - **FDA (Food and Drug Administration)**
- They regulate:
 - Acceptable types and concentrations.
 - Safety limits (based on toxicity studies).
 - Labeling (some preservatives must be declared on packaging).

Toxicity and Adverse Effects

- Preservatives can cause:
 - **Hypersensitivity reactions:** skin rashes, itching, swelling.
 - **Ocular toxicity:** especially with long-term use of eye drops containing BAK.
 - **Systemic toxicity:** e.g., benzyl alcohol toxicity in neonates ("gasping syndrome").
 - **Endocrine disruption:** parabens have been studied for potential estrogenic effects.
- Thus, preservative use must be **justified, minimized, and optimized**.

Classification of Preservatives

Preservatives can be broadly classified based on their mechanism of action or chemical nature.



A. Based on Mechanism of Action:

1. Antimicrobial Preservatives:

- Prevent or inhibit the growth of microorganisms.
- **Example:** Benzalkonium chloride, Phenol, Chlorocresol.

2. Antioxidants (also sometimes referred to as preservatives):

- Prevent oxidation of active pharmaceutical ingredients (APIs).
- **Example:** Butylated hydroxyanisole (BHA), Ascorbic acid.

3. Chelating Agents:

- Inhibit microbial growth by chelating essential metal ions.
- **Example:** EDTA (Ethylenediaminetetraacetic acid).

B. Based on Chemical Structure:

1. Alcohols and Polyols:

- Ethanol, Propylene glycol, Glycerin.
- These work by dehydrating bacterial cells.

2. Acids and Their Salts:

- Benzoic acid, Sorbic acid, Parabens (methylparaben, propylparaben).
- Most effective at acidic pH.

3. Phenols and Phenol Derivatives:

- Phenol, Chlorocresol, Thymol.

- Disrupt cell membranes and precipitate cellular proteins.

4. Quaternary Ammonium Compounds:

- Benzalkonium chloride, Cetylpyridinium chloride.
- Positively charged, interact with bacterial membranes.

5. Mercurials:

- Thiomersal (used in vaccines historically).
- Limited use today due to toxicity concerns.

6. Aldehydes:

- Formaldehyde, Glutaraldehyde.
- High-level disinfectants, rarely used as preservatives due to toxicity.

Preservatives in Marketed Products

Preservative	Chemical Class	Example Brand Name(s)	Dosage Form
Benzalkonium chloride	Quaternary ammonium compound	<i>Xalatan®</i> , <i>Refresh Tears®</i> , <i>Lumigan®</i>	Ophthalmic solution
Benzyl alcohol	Aromatic alcohol	<i>Solumedrol®</i> , <i>Ativan Injection®</i>	Injectable (multi-dose vials)
Phenol	Phenolic compound	<i>Pentothal®</i>	Injectable (anesthetic)
Chlorobutanol	Chlorinated alcohol	<i>Alphagan®</i> , <i>Opticrom®</i>	Ophthalmic solution
Methylparaben + Propylparaben	Parabens	<i>Benadryl® Syrup</i> , <i>Corex-D®</i> , <i>Betnovate®</i>	Oral syrup, topical creams
Sodium benzoate	Benzoic acid salt	<i>Calpol® Syrup</i> , <i>Ascoril®</i> , <i>Zentel® Suspension</i>	Oral liquid
Sorbic acid / Potassium sorbate	Unsaturated fatty acid	<i>Tixylix® Syrup</i> , <i>Otrivin® Paediatric Drops</i>	Oral syrup, nasal drops
Thiomersal (Thimerosal)	Organomercurial compound	<i>BCG Vaccine</i> , <i>Hepatitis B Vaccine (older forms)</i>	Vaccines (multi-dose vials)
Phenoxyethanol	Glycol ether	<i>E45 Cream®</i> , <i>Cetaphil® Lotion</i>	Topical

Note:

- Brand formulations may vary regionally.



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