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A SHORT REVIEW ON: PRESERVATIVE ROLE IN PHARMACEUTICALS AND ITS IMPACT ON HEALTHCARE SYSTEM

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ABSTRACT

Preservatives are compounds that are frequently used in a variety of foods and pharmaceutical items to extend their shelf life. To prevent alterations and deterioration by microbes during storage, preservatives must be added to such items, especially to those with greater water contents. Preservatives are frequently used as ingredients to food, cosmetics, and medicinal items. The nature of several liquid solutions' constituents makes them vulnerable to microbial contamination. Preservatives in this preparation prevent the product from degrading and changing. Preservatives are substances, either natural or artificial, that are applied to a variety of goods to assist stop microbial decay.The study of ideal qualities, categorization, and mechanisms of action, pharmaceutical uses, and its effects on health are the topics covered in the current article.

INTRODUCTION

Preservatives in pharmaceuticals and medicine. Medicines including acetaminophen, insulin, and cough syrup frequently contain preservatives to help prevent microbial infection. Simply said, preservatives work to stop the development of bacteria and fungus, two types of germs that can lead to illness or infection. Preservatives are frequently utilised as additives in cosmetics, food, and medicinal items. Preservatives are used to safeguard this preparation, preventing product deterioration and modification. A preservative is a natural or artificial substance that is applied to a variety of items to assist stop microbial decay. [1]

PRESERVATIVES: To extend the shelf life of different foods and medicinal items, preservatives are frequently applied.

Ideal Properties of Preservatives

1. It doesn't irritate people.
2. It must not be poisonous
3. It needs to be stable both chemically and physically.
4. The preservative employed in formulations should work well with the other substances.
5. It should have a broad range of activity and function well as an antibacterial agent.
6. It must be strong in order to function as a preservative in low concentrations.
7. It must continue to operate during the production, storage, and use of the product. [1,1]

Need for preservatives: To defend against microbial assault on our medicine. To increase the drug's action and effectiveness.

To steady our goods. To extend the product's shelf life. [1]

Preservatives can be categorised in a number of ways, some of which are listed below:

A. CLASSIFICATION BASED ON MECHANISM OF ACTION

1. Antioxidants: The substance that stops active medicinal ingredients from oxidising, which would otherwise cause them to degrade since they are oxygen-sensitive.

Eg. Vitamin C
Vitamin E
BHA (Butylatedhydroxyanisole).
BHT (Butylatedhydroxytoluene).

2. Antimicrobial agents: The substance that fights gram-positive and gram-negative microorganisms that cause medicinal preparations with minimal inclusion levels to degrade.

Eg. Sodium benzoate
Benzoates
Sorbates

3. Chelating agents: Agents that combine with medicinal ingredients to generate complexes that stop formulations from degrading.

Eg. EDTA (Disodium ethylenediamine tetraacetic acid)
Polyphosphates
Citric acid [2,3]

B. CLASSIFICATION BASED ON SOURCE

1. Natural Preservatives: These medications are derived from natural sources such as plants, minerals, animals, etc.

Eg. Sodium chloride (Salt)
Lemon
Neem Oil
Honey

2. Artificial Preservatives: These preservatives were created by humans through chemical synthesis and are mildly toxic to a variety of microorganisms.

Eg. Propionets
Benzoates, Sorbates, nitrites
Sodium benzoate. [2,3]

MECHANISM OF ACTION: preserving in their behaviour? Traditional preservatives include natural ingredients like salt, vinegar, sugar, and diatomaceous earth. Food can also be preserved via techniques including freezing, plucking, smocking, and salting. Another class of preservatives targets vegetable and fruits enzymes that continue to break down after cutting. However, as FDA regulations do not currently mandate that the type of preservative used in vegetable and fruit products be correctly disclosed on the labels. [4]

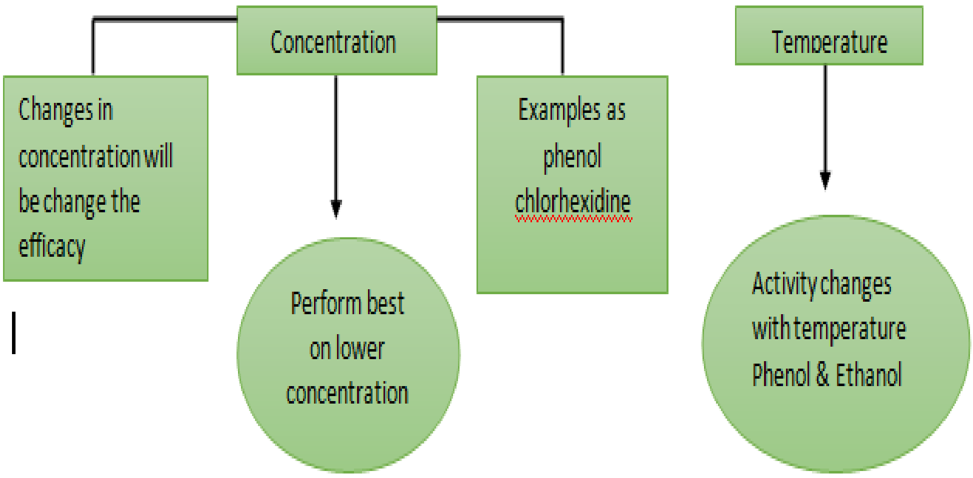

Fig 1: Relationship between Concentration and Temperature

Table 1: Preservative concentration for recommended solid and liquid oral preparation

Preservative	Recommended concentration for solid	Preservative	Recommended concentration for liquid
Chlorobutanol	0.25 - 0.5%	Bornidol	0.001 - 0.05%
Benzalkonium	0.01%	Propyl paraben	0.5 - 0.25%
Phenol	0.065 - 0.02%	Sodium benzoate	0.1 - 0.2%
Benzyl alcohol	0.5 - 10%	Sorbic acid	0.1 - 0.2%
Methyl paraben	0.01 - 0.5%	Methyl paraben	0.25%
		Benzoic acid	0.1 - 0.2%

PRESERVATIVE	SIDE EFFECTS & HEALTH ISSUES	DIFFERENT DOSAGE FORM
Paraben	Potent irritants	**Oral:** methyl, ethyl, propyl parabens, calcium lactate, sodium benzoate, sodium and potassium, sorbic acid
Formaldehyde **Diazolidinyl urea** **Imidazolidinyl urea**	irritation in eye irritation in skin irritation in lung	**Dermal**: benzalkonium chloride, thiomersal, imidurea, phenyl salicylate, chlorhexine, cetrimide, chlorocresol,
Benzyl alcohol	Fatal toxic syndrome	**Dental:** sodium benzoate, potassium sorbate, benzoic acid, chloride, methyl and ethyl parabens, cetyl pyridinium.
Cetyl alcohol **Stearyl alcohol**	Infrequent sensitizers	**Ophthalmic:** benzalkonium chloride, imidurea, thiomersal, chlorhexidine, benzoic acid, sodium perborate, Boric acid, EDTA.
2-phenyl ethanol	Irritant to skin, eyes and Mucous membrane	**Nasal:** benzalkonium chloride, potassium sorbate, EDTA phenyl carbinol, chlorobutanol, chloroxcresol.
Benzoic acid	Gastric irritation	
Chloroxylenol	Cross sensitivity	
Chlorocresol	Irritation in skin Irritation in eye	**Rectal:** benzyl alcohol, sodium benzoate, benzoic acid, chlorhexidine gluconate, methyl hydroxyl benzoate.
Hexachlorophene	Neurotoxicity	
EDTA	Dose-related brocho constriction	

Table 2: Various preservatives side effect and impact on health issues

FACTORS AFFECTING PRESERVATIVES EFFICACY

1. Interaction with formulation
2. Properties of the preservation
3.Effects of containers
4. Type of microorganisms
5. Influence of pH

1. Interaction with formulation: Preservatives can interact with hydrocollids like methylcellulose, aligned, and tragacanth, which lessens their effectiveness. To create beautiful applications, many emulgents are utilised in medicinal formulations. Preservatives and the emulsified oil phase, as well as emulgent molecules, may interact. The type of emulgent, oil water ratio, and nature of the oil all affect how much preservative is needed to safeguard the system. Due to their interactions with additional preservatives, several tablet additives produce issues with tablet preservation.

2. Properties of the preservation: In a multi-phase system, a preservative distribution that is more solubilized in the bulk phase is preferred. If the pH is unfavourable, some compounds, including chlorobutol, may hydrolyze while being stored. Preservatives may lose their antibacterial properties if they interact with chemicals leached from the container.

3. Effects of containers: If the seal is airtight, it is assumed that formulas placed in glass containers would preserve their preservative ingredient. Preservatives could interact with the plastic container by penetrating it. Even though many preservatives react with rubber, it is nevertheless utilised for closures. Pathogen contamination might be brought on via containers or closures. Mold spores commonly come from corks and screw-capped bottles.

4. Type of microorganisms: Products made from plants could have harmful microbes in them. E. g. Bacillus anthracis and Clostridium species. Pharmaceutical items may become spoiled as a result of these soil microbes. Salmonella typhi and other pathogens may be present in many goods made from animal sources. From geletin, tetanus and gas gangrene spores have been identified.

5. Influence of pH: The chemical stability and the preservative's action may both be impacted by changing the pH of the solution. While cationic active quaternary ammonium compounds are more active at high pH levels, the bulk of preservatives are less pH dependant. [5]

EVALUATION OF PRESERVATIVES:

Preservatives have typically been assessed using time-consuming tests:

- ✓ AET (PHARMACOPOEIAL ANTIMICROBIAL EFFECTIVENESS TESTS)
- ✓ PET (PRESERVATIVE EFFICACY TESTS)

These are necessary for evaluating the antimicrobial preservation of medicinal items with numerous uses.

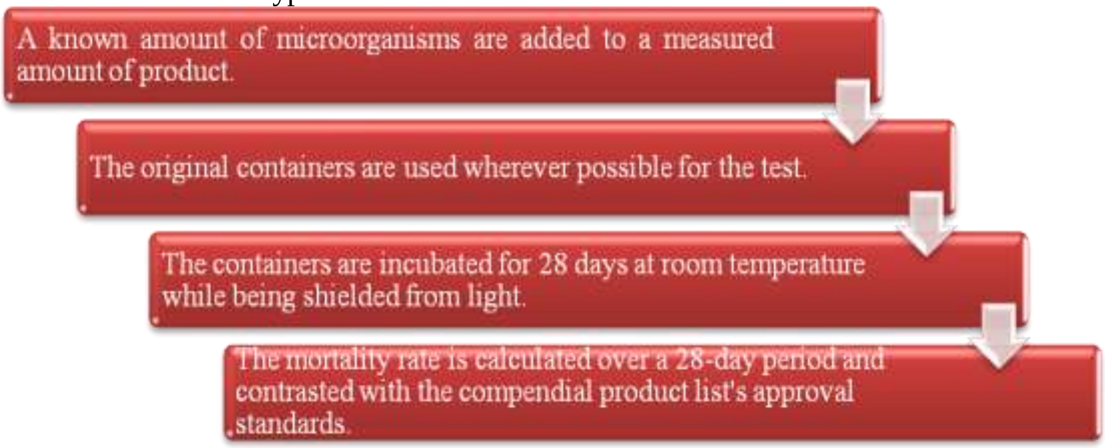

Fig 2: Process of Antimicrobial Effectiveness Tests

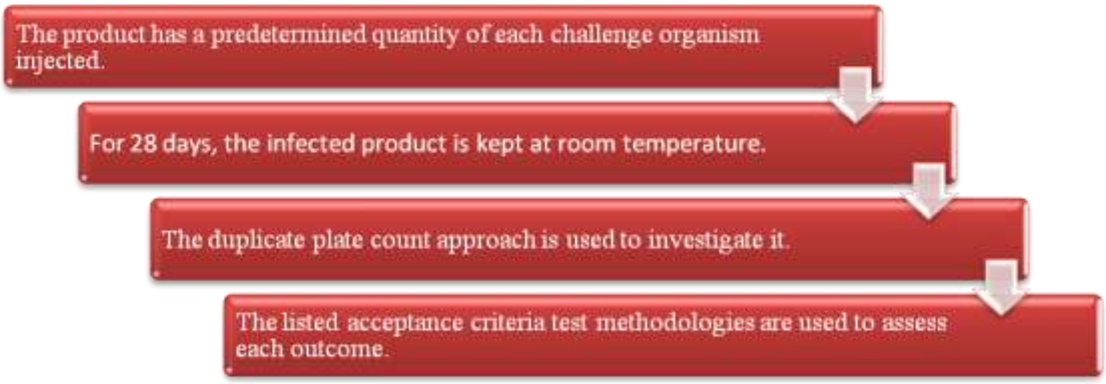

Fig 3: Process of Preservative Efficacy Testing

ANTIMICROBIAL EFFECTIVENESS TESTS (AET): The efficiency of preservative systems in multidose dosage forms is assessed using this test. Originally intended to assess how well antimicrobials applied to products to prevent the development of microorganisms that could be introduced during or after the manufacturing process performed [5]

PRESERVATIVE EFFICACY TESTING (PET):

In such testing, a product is exposed to a certain number of colony forming units (CFU) of various test microbs (yeasts, fungiand bacteria), counted at time zero, and the survival / kill rate is subsequently observed at predetermined intervals up to 28 days. [5]

ANALYSIS OF PRESERVATIVES IN PRODUCTS:

- High performance Liquid chromatography,
- Thin Layer chromatographic methods and
- Gas chromatography methods,
- atomic absorption spectroscopic method (AAS)
- Capillary electrophoresis (CE),

Analysis of preservatives in pharmaceutical products

To extend the shelf life of different foods and medicinal items, preservatives are frequently applied. Preservatives must be added to such goods, especially those with a greater water content, in order to prevent microbial alterations and deterioration during storage. 1-3 In order to create the proper dosage form of a pharmacological agent, other components are also used. Some of these substances may be added to the product to give it the necessary physical and chemical properties or to enhance its flavour, aroma, and appearance. The additional substance must always be safe in the quantity used and never go above the bare minimum needed to get the desired effect. Its presence has no negative effects on the official preparation's bioavailability, therapeutic effectiveness, or safety, and it has no negative effects on the analyses and testing that are required to check for pharmacopeial compliance. [7]

Analysis of Preservatives: To avoid change and degradation of the product formulations, medicines, cosmetics, biological samples, food, wood, and plastics goods frequently utilise a single preservative, but more frequently mixtures of preservatives. Due to their propensity to cause allergic contact, these preservatives might be dangerous to consumers. Therefore, it is crucial to simultaneously assess these preservatives in commercial pharmaceutical goods for both quality control and customer safety. Since interferences from other components might cause issues, analytical techniques created for the measurement of preservatives in these matrices are often built to address them. Preservatives are typically found as tiny components in complicated matrices due to the circumstances under which they are utilised in pharmaceutical goods. Preservatives in food, wood polymers, biological samples, and cosmetics have been the subject of several reviews. With the exception of Ho and Chen's review, which was published in Chinese, the literature is lacking in a thorough investigation of preservatives as a group in pharmaceutical goods. Preservatives in pharmaceutical goods are the focus of the current review. [8]

Methods for analysing of preservatives

High performance liquid chromatographic methods

If complicated samples are involved, high performance liquid chromatographic procedures (HPLC) are without a doubt the best methodology. Therefore, a number of HPLC techniques were published for the detection of parabens in pharmaceuticals. The most typical setup for the analysis of parabens in pharmaceutical and cosmetic items uses regular or silanol-deactivated C18 or C8 columns paired with UV detection. Only the most modern HPLC techniques for detecting parabens in diverse medicinal items are discussed in this study. [9,10]

Gas chromatographic methods: Gas chromatography (GC) is advised by the US Pharmacopoeia for the FID-based determination of parabens as preservatives. For the purpose of identifying parabens in antacid products, De-Croo et al. utilised GC. Extracting the parabens was followed by a procedure with hexamethyldisilazane and heptafluorobutyric anhydride to derivatize them. Using the same methodology and other derivatizing agents, many techniques Parabens and their derivatives can be determined using this method have been published. [11]

Thin layer chromatographic methods: For the detection of parabens in pharmaceutical items, a number of TLC and HP-TLC techniques have been published. A TLC technique is prescribed by European Pharmacopoeia 22 for the identification of parabens in medicinal substances. Using TLC and a combination of n-pentane and glacial acetic acid as the mobile phase, parabens in antibiotic peptides such as polymixin B sulphate, neomycin sulphate, and zinc bacytracin ointments were identified. A 260 nm densitometry measurement was used for detection. Similar to this, RP-TLC plates were used to measure the parabens in the antacid solution. Densitometry analysis at a wavelength of 254 nm was used for detection. [12]

Flow injection analysis:

The measurement of methyl paraben, ethyl paraben, propyl paraben, and butyl paraben in food, pharmaceuticals, and cosmetics has recently been reported using the flow injection-chemiluminescence (FIA-CL) technique. In strong sulphuric acid, parabens enhance the chemiluminescence reaction between cerium (iv) and rhodamine, leading to the development of the technique. The approach has a large dynamic range and extremely low detection limits. [13]

PRESERVATIVES	METHOD	MOBILE PHASE	WAVELENGTH
Paraben	RP - HPLC	Methanol and phosphate buffer pH 7.05	254nm
Methyl & propyl paraben& hydrocartisone	RP - HPLC	Methanol – acetonitrile &Water	238nm
Paraben & diclofenac Sodium	RP - HPLC	pH – 2.5	238nm
Paraben with ambroxol	RP - HPLC	pH – 3.45 with glacial acetic acid	247nm
Parabenfrom metronidazole benzoate	RP - HPLC	Acetonitrile phosphate buffer pH-7.0	260nm

Medicinal product	Preservative
Oral	Methyl, ethyl, propyl parabens and combination. potassium sorbate, benzoic acid, sorbic acid, propionic acid, Sodium benzoate, methyl paraben /sodium benzoate Combination.
Topical (including nasal)	Benzyl alcohol, cetyl alcohol, steryl alcohol, imidurea, bronopol, chlorhexidine. Benzalkonium chloride, benzethonium chloride, cetrimonium bromide, benzoic acid, sorbic acid, Methyl parabens, ethyl parabens, propyl parabens and combination.
Parenteral (Including vaccines)	chlorbutanol,2-ethoxyethanol, Benzyl alcohol, 3-cresol, benzoic acid, phenol, thimerosal, phenylmercurate salts, sorbic acid.
Ophthalmic	Sodium benzoate, Benzalkonium chloride, benzoic acid, imidurea, chlorhexidine,polyaminopropylbiguanide,polyhexamethylbiguanide, potassium sorbate, EDTA, sorbic acid.

Table 4: Preservatives Used in Various Dosage Forms

CONCLUSION

Physical, chemical, and microbiological stability should be maintained throughout the shelf life and use of all medications and pharmaceuticals delivered to patients. To verify the safety and quality of all medications in every dose form, analysis should be performed. As we've seen, natural preservatives have fewer adverse effects than synthetic preservatives, which are used to preserve foods, cosmetics, and other products. We can easily employ natural preservatives because they are more affordable and readily available. Natural preservatives prolong the shelf life of the substance they are applied to in addition to decreasing bacterial development. Additionally, it prevents any hazardous effects and enables them to keep their consistency or remain fresh for an extended period of time. Although research has shown that synthetic preservatives can also be beneficial, virtually all of them are naturally carcinogenic, which leads to a number of health issues. As a result, they must be used while taking into account the maximum safety limit for the preservatives used in both medications and cosmetics. These systems still do not function or cost as well as conventional preservatives, which is why they are not frequently utilised in commercially available goods. Therefore, since natural preservatives have so many positive benefits, it may be preferable to utilise them rather than synthetic ones.

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