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A Review: Preservations of Pharmaceutical Products

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ABSTRACT
Pharmacist have been aware of the need to protect their products against microbial contamination but it is only during the last one or perhaps two decodes the serious throughout of has been applied to the science of preservations. The addition of preservatives to such products, especially to those that have higher water content is essential for avoiding alternation and degradation by microorganisms during storage. Demonstration of antimicrobial preservative effectiveness is required for these functional excipient. This article reviews key factors for consideration in the selection of preservatives, principles of the preservative-effectiveness test.

Keywords: Preservatives, Microbial Contamination, Alternation and Degradation.

I. INTRODUCTION

An antimicrobial agent (preservative) is the chemical substance used to improve shelf life of drug or formulations and inhibit the growth of microbes and reduces the risk of spoilage of pharmaceutical products. The main functions of antimicrobial preservatives is to prevent the growth of unwanted microorganism in pharmaceutical preparations. The correct approach to prevention has as its foundation in two important principles:

– The first of these is that the addition of a preservative to a product must not be done to.
– The preservative should be an integral part of the formulation, chosen to afford protection in that particular environment.

A single preservative is not suitable for preservation of all pharmaceutical formulations, combination of two or more preservations are used to extend the range and spectrum of preservation. Preservative are widely employed in pharmaceuticals dosage forms such as emulsions, suspensions, semisolids, parenteral preparations, etc, …

II. DISCUSSION

Pharmaceutical products are substances or mixtures intended for use in humans for diagnosing, treating, 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 preserved during storage and multidose 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 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

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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 products tolerance or safety.

Chemical preservatives used in pharmaceutical formulations

Formulations	Preservatives	Concentrations (%w/w)
Tablets	Methyl paraben	0.1
Injections	Phenol Cresol Benzyl alcohol Thiomersal Methyl hydroxybenzoate	0.2- 0.60.20.51.0- 2.0 0.01 0.1
Eyedrops	Benzalkonium chloride Phenyl mercuric nitrate Chlorhexidineacetate	 0.010. 0020. 01
Liquids/ mixtures	Bronopol Alcohol Methyl paraben Chloroform Benzalkonium chloride chlorocresol	0.215- 200.10 .25 0.005- 0.020.1
Semisolids	Chlorocresol Dichlorobenzyl alcohol Cetyrimethyl ammonium bromide	0.2 0.1- 0.20.005- 0.1

Classification of Preservatives:

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

a) Antioxidant- As active pharmaceutical ingredients are sensitive to oxygen, antioxidants prevent them from oxidizing.

b) 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. Sorbate, Benzoate, and Sodium benzoate are examples.

c) Chelating agents- Chemical agents are those capable of forming complexes with pharmaceutical ingredients and preventing degradation of the pharmaceutical formulation. The following are examples: EDTA, polyphosphates, and citric acid.

2. Classification Based on Source

A) Natural Preservatives: They are primarily used in foods and beverages to help reduce rotting and preserve the items color and flavor. However they are also found in cosmetics and other hygiene products. Common examples of natural preservatives include; Aloe vera, Citric acid, Lemon juice, Sugar.

B) Artificial/ Chemical Preservatives: They are manmade substances that are added to numerous products to extend their shelf life, While they are created to prevent foods from spoiling and help

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them retain their shape and color, they are offentimes filled with chemicals. Common examples of chemical preservatives include; Antimicrobial agents, Antioxidant, Benzoates.

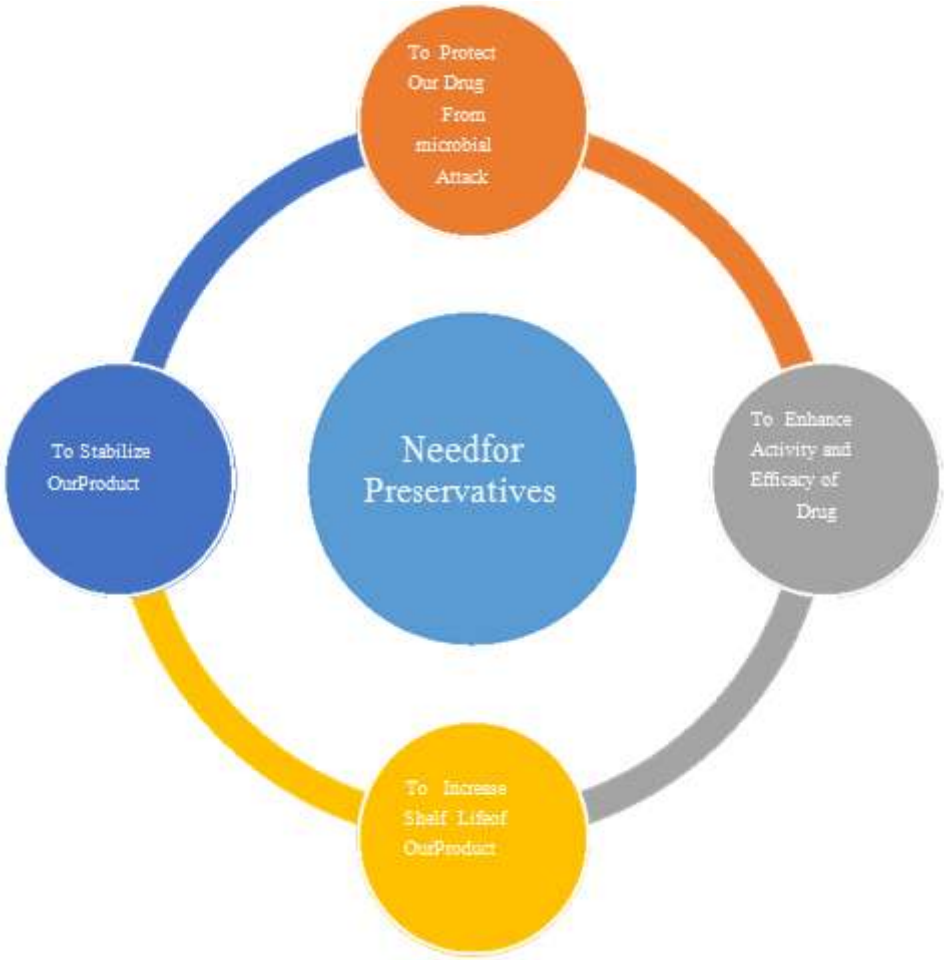
Mechanism of Action:

- Natural substances such s salt, sugar, vinegar and diatomaceous earth are also used as traditional preservatives.
- Certain processes such as freezing, pickling, smoking and salting can also be used to preserve food.
- Another group of preservatives targets enzymes in pharmaceutical products that continue to metabolize.

Ideal properties of preservatives:

i. Should able to kill all the microbes contaminants rapidly.
ii. Tasteless and odourless.
iii. Not be irritant.
iv. Non-toxic to the patient.
v. Physically and chemically stable.
vi. Effective at low concentration throughout the life of the medicine.
vii. Should be selective in reacting with the contaminants and not the ingredients of the medicine.
viii. Cost effective.

Need For Preservatives:



Development of a Preservative System.

- A single preservative is not found to possess all the ideal requirements of a preservative.
- Even some microbes like Pseudomonas have already started showing resistance to many of the present preservatives.
- Hence a combination of preservatives is preferred instead of using a single preservative.

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- By combining two preservatives Synergy can be obtained means increased inhibitory effect, e.g. Methyl para hydroxybenzoic acid is combined with propyl para hydroxybenzoic acid in ratio of 10:1.
- By combining the preservatives spectrum of activity of the system gets widened e.g. eye drops and contact lens cleaners combine "Phenoxetol with Phenyl ethyl alcohol and Benzalkonium Chloride.
- Preservative Germall 115 is an antibacterial when combined with parabens the combination becomes antibacterial as well as antifungal.
- However, the combination system when used should have enough half lifes with reference to the life of the formulation.

Factors Affecting Preservatives Efficacy

1. Interaction with formulation

- Hydrocollids such as methylcellulose, alignates, tragacanth can interact with preservatives and diminish their activity.
- Many emulgents are used in pharmaceutical preparations to produce elegant applications. Interaction may occur between preservatives and emulsified oil phase and with emulgent molecules.
- Nature of oil, oil water ratio, type of concentration of emulgent, influence the concentration of preservatives needed to protect the system.
- Many tablet additives cause problems in tablet preservations due to their interaction with added preservatives.

2. Properties of the preservation

- The distribution of preservative must be homogenous and more solubility in the bulk phase is preferable in multi-phase system.
- Some chemicals such as chlorobutol may hydrolyse on storage if the pH is unfavourable.
- Preservatives may react with substances leached from the container and lose its antimicrobial activity.

3. Effects of containers

- Formulations packed in glass containers can be expected to retain their preservative content if closure is airtight.
- Preservatives may penetrate through the plastic container and interacts with it.
- Rubber also reacts with many preservatives but is still used for closures.
- Containers or closures may cause contamination of pathogens.
- Screw-capped containers and corks are the common source of mould spores.

4. Type of microorganisms

- Plants products may contain pathogenic microorganisms from the soil. E.g. Clostridium species, Bacillus anthracis.
- These soil microorganisms can cause spoilage of pharmaceutical products.
- Many products prepared from animal sources may contain pathogens like Salmonella typhi.
- Spores of tetanus and gas gangrene have been isolated from gelatine.

5. Influence of pH

- Adjustment of the pH of solution may affect the chemical stability and the activity of the preservative.
- The majority of preservatives are less dependent upon pH, although cationic active quaternary ammonium compounds are more active at high pH values.

Evaluation of microbial stability of formulation: Preservative efficacy test

This is applied to the formulated medicines in its final container to determine whether it is protected against microbial spoilage. It is used to determine the stability of multiple dose such as parenteral, oral, nasal, topical and ophthalmic products made with aqueous bases or vehicle. It is used to check the effectiveness of antimicrobial preservatives. These pharmaceutical formulation also evaluated at time to time [once evaluated under 6 months]. The test and standard apply only to the product in the original, unopened container, in which it is supplied by manufacture.

Medium used - for the initial cultivation of test microorganism, use soyabean casein digest agar medium.

Choice of test microorganisms and inoculum preparation

The intension is to use microorganisms which are likely to arise in the raw material used in the product and which occurs in the manufacturing environment and represent a particular health hazard, if they grew in the production. The test microorganism used for preservative efficacy tests are, Staphylococcus aureus ATCC 6538, Pseudomonas aeruginosa ATCC 9027,Escherichia

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coli ATCC 8739, Candida albicans ATCC 10231 and Aspergillus brasiliensis ATCC 16404. Fresh stock culture of each test microorganism is subcultured on the surface of soyabean casein digest agar medium. Incubate the bacterial culture at 3035*c for 18-24 hours. Using sterile saline solution, harvest the bacteria and dilute suitability with sterile solution to bring the count to about $1x10^8$ CFU/ml.

Procedure

-Incubate each original product container with one of the standardised microbial suspension using a ratio equivalent to 0.1 ml of inoculum suspension to 20ml product and mix.

-Final concentration should be $1x10^5$ – $1x10^6$ microbes per ml of products.

-Determine the number of viable microorganism by the plate count method and calculated, the initial concentration of microbes per ml.

-Incubate the inoculate containers or tubes at room temperature.

-Determine the viable count by the plate count method at 7,14 and 24 day subsequent to inoculation. Calculation the percentage of reduction in CFU per ml for each organism at the states test intervals and express the change in terms of percentage of initial concentration.

CFU [colony- forming unit]

Interpretation of Results

For parenteral, ophthalmic, sterile nasal & otical preparations

Concentration of viable bacteria is not more than 10% of initial construction of 7 days and not more than 0.1% of initial concentration at 14 days and there is further decrease in count at 28 days.

For topical preparation

Concentration of viable bacteria is not more than 1% of initial concentration at 14 days and there is further decrease in count at 28 days. For oral preparations

Not more than 10% of the initial concentration at 14 days and further decrease in count at 28 days.

III. CONCLUSION

Current industrial food processes have available a broad array of techniques and chemical synthesis additives for their use in food preservation. A preservative is considered necessary to keep the food protected but we should be aware whether we do benefit from the system or not. Few people debate that preservatives are necessary to keep but it is the extent of preservatives use that has become a point of debate. Since there are many effective and potential uses of using natural and chemical preservatives in different ingredients. Satisfactory evidence of its effectiveness and safety is still lacking.

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