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ECOSYSTEM IMPACTS OF SYNTHETIC AND NATURAL PRESERVATIVES: FOCUSING ON CONSUMPTION PATTERNS AND THEIR INFLUENCE ON THE ENVIRONMENT

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ABSTRACT

Preservatives are important ingredients in pharmaceutical preparations. They are used to maintain the integrity and efficacy of pharmaceuticals by inhibiting the growth of organisms and also by extending the shelf life of preparations. The preservatives are categorized based on their function and chemical composition, which helps in making logical decisions when developing medications and ensure that the appropriate preservatives are used for microorganisms and product compositions. The development of natural and eco-friendly preservative alternatives has been stressed in recent trends. As the pharmaceutical industry grows, research and development efforts are directed toward developing novel preservatives and creative preservation techniques. Pharmaceutical companies must strike a balance between meeting preferences and ensuring the safety and stability of their products. Environmental considerations regarding the disposal of pharmaceutical preservatives are also paramount. Proper disposal and management strategies are necessary to minimize their environmental impact and prevent adverse effects on the ecosystem. The safety and effectiveness of pharmaceutical goods continue to be the key factors in the use of preservatives, even as the industry navigates changing customer preferences and environmental concerns. This paper discusses about preservatives, types of preservatives, the latest consumer trends and technologies adopted by various pharmaceutical industries, and its environmental impacts.

KEYWORDS

Preservatives, *In-vitro and In-vivo*-preservative, Ecosystem, Pharmaceutical products, Marketing analysis, Regulatory aspects and Future concerns.

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INTRODUCTION

Preservatives are crucial ingredients in pharmaceutical preparations. They preserve the integrity and efficacy of pharmaceuticals, particularly those in liquid form or prone to contamination, by inhibiting the growth of organisms and guaranteeing the stability and safety

of the medicines[1]. A pharmaceutical product's pH, compatibility with other components, and the microorganisms it is intended to inhibit must all be taken into account when choosing a preservative. In addition, it is crucial to precisely ascertain the right preservative concentration to attain the intended antibacterial outcome without jeopardizing the product's stability or safety[2]. Preservatives are essential for extending the shelf life of medicinal items as well as for inhibiting microbiological growth. Ensuring the overall efficacy of the product requires a thorough understanding of the preservative's mode of action and how it interacts with other ingredients in the formulation[3]. It's critical to understand the differences between *in vivo* and *in vitro* preservatives while creating pharmaceutical products. Preservatives in vivo, including those used in injectable drugs or ophthalmic solutions, are made to stop microorganisms from growing inside the body[4]. To make sure these preservatives won't damage the body's tissues or organs, they must be carefully chosen and evaluated. Benzalkonium chloride, phenylmercuric nitrate, and chlorobutanol are examples of in-vivo preservatives frequently found in pharmaceutical products[5]. *In vitro* preservatives, on the other hand, stop microorganisms from growing in non-sterile formulations such lotions, ointments and creams. Pharmaceutical items frequently contain methylparaben, propylparaben, phenoxyethanol and benzalkonium chloride as *in-vitro* preservatives. The development of natural and eco-friendly preservative alternatives has been stressed in recent trends for pharmaceutical products. Pharmaceutical businesses are looking at substitutes for conventional synthetic preservatives as consumer demand for natural and eco-friendly products grows. Because of their antibacterial qualities and low environmental effect, natural preservatives like organic acids, plant-derived essential oils, and antimicrobial peptides are becoming more and more well-liked[6]. Preservatives are also being used at lower quantities to reduce the possibility of adverse effects and maintain efficient microbiological control. In response to changing customer preferences and regulatory requirements, the pharmaceutical industry is progressively adopting these new preservative trends into product formulations as research and development in this field continues.

Preservatives are necessary to ensure the stability and safety of pharmaceutical products, yet there is rising worry regarding these substances' possible adverse effects. Preservatives have been connected to a number of allergic reactions and skin irritations, especially in those with sensitive skin[7]. Furthermore, because preservatives may have an adverse effect on aquatic environments and species when these goods are subsequently disposed of, their use whether *in-vitro* or *in- vivo* has sparked environmental concerns. The diversity of living things and the balance of ecosystems can be significantly impacted by the buildup of artificial preservatives in the environment[8]. An upward trend in customer preferences toward safer and more sustainable solutions is reflected in the rising demand for natural and eco-friendly products. Therefore, in order to meet these changing expectations of consumers, pharmaceutical companies should give priority to the research and application of natural preservatives. Companies can show their dedication to environmental responsibility and public health by using natural alternatives in addition to meeting regulatory requirements[9]. Research into the creation of novel preservatives and inventive preservation methods is ongoing as the pharmaceutical industry changes. With the goal of guaranteeing the safety, effectiveness, and lifespan of pharmaceutical products, these developments seek to overcome the unique difficulties related to their preservation[10].

VARIOUS PRESERVATIVES IN PHARMACEUTICAL PRODUCTS

The pharmaceutical industry may make rational choices when creating medicines and guarantee the right choice of preservatives for the targeted microorganisms and product formulations by classifying preservatives according to their intended use and chemical composition.

TYPES OF PRESERVATIVES COMMONLY USED IN PHARMACEUTICAL PRODUCTS

Based on mechanism of action

Antimicrobial preservatives

These kinds of preservatives work well against a wide range of microorganisms, such as yeast, fungus, and bacteria. Antimicrobial preservatives such as thimerosal, chlorhexidine, and benzalkonium chloride are frequently used. Because of the increased danger of microbial contamination resulting from repeated usage and the introduction of germs during administration, these preservatives are essential for multidose formulations, such as eye drops and injectable drugs[11].

Antioxidants

Antioxidants are essential for preventing oxidation-induced medicinal product deterioration. Antioxidants work by preventing oxidation, which helps keep drugs that are susceptible to oxidative deterioration-like some parenteral and liquid oral formulations-stable and effective. A few examples of these include ascorbic acid, butyl hydroxy anisole (BHA), and butyl hydroxytoluene (BHT) are few examples of antioxidant preservatives[12].

Chelating Agents

These preservatives function by ensnaring metal ions, such calcium and magnesium, which have the ability to accelerate the deterioration of medicinal goods. By averting the unfavourable consequences of metal ion-catalyzed reactions, these compounds aid in maintaining the general safety and quality of the product[13].

pH Adjusters

These agents are essential in bringing pharmaceutical formulations' pH values down to a level that prevents the growth of microorganisms. pH adjusters aid in the overall preservation of the goods by generating an unfavourable environment for bacteria. A few popular pH adjusters found in pharmaceutical products as preservatives are phosphoric acid, sodium citrate, and citric acid[14].

FACTORS AFFECTING PRESERVATIVE ACTION

Interaction with formulation

Hydrocolloids like methylcellulose, alginates, and tragacanth have the potential to reduce the effectiveness of preservatives through their interaction.

Several emulsifiers are utilized in the formulation of pharmaceutical products to create refined applications. There is a possibility of interaction between preservatives and the emulsified oil phase, as well as with emulsifier molecules.

Preservative concentrations required to safeguard the system are influenced by several factors such as the type of oil, oil-to-water ratio, and emulgent concentration.

Many tablet additives can create challenges in preserving tablets because of their interaction with additional preservatives.

Properties of the preservation

Some substances like chloro-butanol may undergo hydrolysis during storage if the pH conditions are not favourable.

Preservatives can interact with compounds that have seeped from the container and diminish their antimicrobial effectiveness.

Effects of containers

Preservatives have the potential to seep through the plastic container and react with it.

Rubber still interacts with a variety of preservatives but continues to be utilized for closures.

Containers or closures have the potential to lead to contamination by pathogens.

Screw-top containers and cork closures are frequently responsible for mold spores.

Type of microorganisms

Plant products may harbor harmful microorganisms from the soil. E.g. Clostridium species, Bacillus anthracis. These soil microorganisms have the potential to spoil pharmaceutical products.

Many animal-derived products may harbour pathogens such as Salmonella typhi.

Influence of pH

Adjusting the pH of a solution can influence both the chemical stability and effectiveness of the preservative.

The majority of preservatives are not strongly influenced by pH, although cationic active quaternary ammonium compounds exhibit higher activity at elevated pH levels[11].

ADVERSE EFFECTS OF DRUG PRESERVATIVES

Preservatives in pharmaceuticals are essential for preventing microbial contamination and ensuring the stability of medication. However, some people may encounter negative responses to specific preservatives, which can range from mild to severe and manifest as local or systemic effects.

Benzyl Alcohol

Adverse Effects

Benzyl alcohol has the potential to trigger hypersensitivity responses, such as skin irritation and contact dermatitis. Benzyl alcohol in injectable forms has been linked to a rare yet severe condition known as "gasping syndrome" in newborns, which is marked by metabolic acidosis, breathing difficulties, and central nervous system depression[15].

Phenol

Adverse Effects: Phenol has the potential to induce local irritation and tissue harm at the site of injection. Systemic toxicity may manifest if phenol is absorbed in substantial quantities[16].

Benzalkonium Chloride

Adverse Effects: Benzalkonium chloride, often found in ophthalmic solutions, can lead to eye irritation and allergic responses in certain people. Its prolonged use might also result in dry eye symptoms[17].

Methylparaben and Propylparaben: Adverse Responses

Certain people might have a sensitivity or an allergic reaction to parabens. Skin responses such as irritation, itching and rash can take place. Parabens could also lead to contact dermatitis in specific individuals[18].

Chlorobutanol

Chlorobutanol may lead to irritation at the application site and could potentially cause dryness of mucous membranes. Hypersensitivity reactions are also possible in certain instances[19].

Sodium Benzoate

Adverse Effects

Sodium benzoate, often utilized as a preservative in oral drugs, has the potential to trigger hypersensitivity responses. Certain people may also have sensitivity to benzoates and manifest allergic reactions[20].

Sorbic Acid

Sorbic acid, when used in topical products, has the potential to induce skin irritation or provoke allergic responses in certain people[21].

IN-VITRO AND *IN-VIVO*: PRESERVATIVE APPLICATIONS

Based on how they are utilized, pharmaceutical product preservatives can be divided into two groups: "*In-vitro*" and "*In-vivo*". Especially in liquid and semi-solid preparations, in-vitro preservatives are employed to stop microbiological growth and preserve the stability of pharmaceutical formulations while they are being stored. Preservatives of this kind, like methylparaben and phenoxyethanol, are added to topical aqueous formulations to prevent the growth of germs that could contaminate the product. Preservatives that are utilized in-vivo are used to stop microbiological contamination and the body from breaking down medicinal items[23].

Pharmaceutical products frequently use benzalkonium chloride, phenylmercuric nitrate, and chlorobutanol as in-vivo preservation[5]. Injectable solutions, ophthalmic preparations and other products that come into direct contact with the body.

Natural-based Preservative

The investigation of natural-based preservatives in pharmaceutical formulations has been prompted by consumer desire for eco-friendly and natural products. Because of their intrinsic antibacterial qualities, organic acids, antimicrobial peptides, and

essential oils derived from plants have all been found to be efficient natural preservatives[24].

These natural substitutes reduce the negative effects that conventional synthetic preservatives have on the environment while also ensuring efficient microbiological control[25].

Alternative Preservation Strategies

The pharmaceutical business has been giving more attention to alternative preservation techniques such aseptic processing and hurdle technology, in addition to the creation of new preservatives. Using a variety of preservation techniques, including pH, temperature, and preservatives, hurdle technology works to establish an environment that is not conducive to the growth of microorganisms. On the other hand, aseptic processing aims to preserve pharmaceutical products' sterility by avoiding microbiological contamination during the production and packaging procedures[26].

EMERGING TRENDS IN PHARMACEUTICAL PRESERVATIVES

New trends in pharmaceutical preservatives are emerging to address the issues involved with preserving pharmaceutical products as a result of the continually changing pharmaceutical business. As customer demand for ethical and ecologically responsible products rises, one noteworthy trend is the development of more natural and eco-friendly preservative solutions. Plant extracts, essential oils and other naturally occurring materials with antibacterial qualities are the sources of these natural preservatives. Combination preservatives, which combine many preservatives to increase efficacy and increase the range of antimicrobial action, are another new trend in preservative usage. Additionally, preservatives can be made with more targeted antibacterial action, focusing on particular kinds of microbes or biofilms[27].

Natural and Environmentally Friendly Preservatives

Pharmaceutical businesses are looking more and more into natural alternatives for preservatives, like organic acids, essential oils and antimicrobial peptides. Because of their antibacterial qualities and low environmental impact, these natural preservatives are becoming more and more well-liked. Pharmaceutical businesses may demonstrate their commitment to environmental stewardship and public health while also keeping up with changing customer tastes by using natural alternatives[28].

Lower Concentrations and Minimizing Side Effects

There is a focus on utilizing preservatives at lower quantities to reduce potential side effects while maintaining efficient microbiological control, in addition to the shift towards natural preservatives. This method tackles worries regarding the possible negative effects of preservatives, like allergic reactions and skin irritations, especially in people who already have sensitivities, allergies, or skin irritations.

Ongoing Research and Development

New preservatives and inventive preservation methods are the focus of continuous research and development efforts as the pharmaceutical business advances. These developments are intended to meet regulatory requirements and satisfy consumer demands for safer and more ecologically friendly options while ensuring the lifetime, safety and effectiveness of pharmaceutical products.

Combination preservatives

Using several preservatives in tandem to increase efficacy and extend the range of antibacterial action is a trend in pharmaceutical preservation. This method is intended to give thorough microbiological control while addressing the shortcomings of specific preservatives[29].

Targeted preservatives

The development of preservatives with more focused antibacterial action, aimed at specific microbes or biofilms, is the result of advancements in preservation techniques. By precisely controlling microbial contamination, this focused strategy enhances the overall safety and effectiveness of medicinal products.

Pharmaceutical businesses keep researching and developing new preservatives in response to consumer preferences for safer and more environmentally friendly choices. The industry is

dedicated to offering safer preservative choices and improved preservation procedures for pharmaceutical products by keeping up with changing consumer needs and regulatory requirements.

By staying abreast of these emerging trends in pharmaceutical preservatives, organizations can establish a leading position in the field of innovation and address the changing requirements of both consumers and regulatory standards.

MARKET ANALYSIS OF PRESERVATIVE USE IN PHARMACEUTICALS

According to market analysis, the use of preservatives in the pharmaceutical sector is projected to experience substantial growth in the near future, fueled by various factors such as rising demand for pharmaceutical goods, advancements in preservation techniques and regulatory requirements for product safety.

Demand and Growth Factors

The demand for pharmaceutical preservatives is expected to increase due to the rising global population, higher incidence of chronic diseases and the expansion of the pharmaceutical industry into emerging markets. Additionally, as the awareness of healthcare and disease prevention grows, the need for safe and effective pharmaceutical products will drive the demand for preservatives.

Advancements in preservation techniques, including the development of natural and environmentally friendly preservatives, are also contributing to the growth of the market. The shift towards natural preservatives derived from plant extracts, essential oils, and organic acids reflects the industry's response to consumer preferences and the global trend towards sustainable and clean label products[30].

Smart Packaging Technology

The integration of smart packaging technology in the pharmaceutical industry is revolutionizing preservative strategies. Smart packaging features antimicrobial surfaces and indicators that can detect and signal the presence of microbial contamination, thereby contributing to the overall safety and quality of pharmaceutical products. This innovation addresses the need for real-time monitoring of product integrity and enhances consumer confidence in the safety of pharmaceutical products.

The market analysis of pharmaceutical preservatives indicates a significant growth trajectory driven by factors such as increased demand for pharmaceutical products, advancements in preservation techniques and the integration of smart packaging technology. The evolving landscape of pharmaceutical preservatives underscores the industry's commitment to meeting consumer demands for safer and more sustainable options while ensuring the safety and efficacy of pharmaceutical products.

Furthermore, the global market for pharmaceutical preservatives is witnessing a move toward sustainable and environmentally friendly solutions. This shift is motivated by rising environmental awareness and an expanding concern emphasis on using natural and renewable resources[31].

REGULATORY ASPECTS FOR PRESERVATIVE USAGE

Regulatory guidelines play a crucial role in dictating the usage of preservatives in pharmaceutical preparations. These regulations outline the types and allowable concentrations of preservatives that can be used to ensure product safety and efficacy. Additionally, these guidelines also address the maximum acceptable limits of preservatives in pharmaceutical products to mitigate potential health risks and adverse effects on patients[32].

Safety and Toxicology

Preservatives need to demonstrate their safety at the proposed level of exposure. Toxicological information should confirm that they are safe for use in medications for various populations, including children and the elderly.

Efficacy

Preservatives must effectively combat a wide range of potential impurities, including bacteria, fungi, and yeast. The effectiveness of the preservative

needs to be proven within the particular product formulation.

Concentration and Usage Levels

Regulations define the highest acceptable levels of preservatives to reduce toxicity and prevent microbial growth, which may differ based on the method of administration. (e.g., oral, topical, ophthalmic).

Stability

Preservatives need to retain their effectiveness throughout the storage duration of the pharmaceutical item under different environmental conditions[33].

Compatibility

Preservatives must not create adverse interactions with other elements of the drug formulation, such as active pharmaceutical ingredients and excipients, which could impact the safety, effectiveness, or stability of the drug[34].

Labelling

The product packaging must accurately display information about the preservative used, including any cautions regarding potential side effects or allergic reactions.

Environmental Impact

The FDA's emphasis is shifting towards the environmental effects of pharmaceuticals, such as preservatives, after they are discarded, although not directly linked to patient safety. It is important to consider the potential environmental impact of preservatives used in pharmaceutical products[35].

Safety Profiles of Common Pharmaceutical Preservatives

Commonly used pharmaceutical preservatives have different safety profiles, and their usage depends on the specific formulation and intended use of the product. Examples of commonly used pharmaceutical preservatives include: benzyl alcohol, methylparaben, propylparaben, chlorobutanol, phenyl ethanol and sodium benzoate. These preservatives have been extensively studied for their safety and efficacy in preserving pharmaceutical products. They have been found to have a broad antimicrobial spectrum, good stability, and non-volatility, making them suitable for use in various formulations.

CONSUMER TRENDS IMPACTING PRESERVATIVE CHOICES IN PHARMACEUTICALS

In line with the growing demand for natural and environmentally friendly products, consumer trends are shaping the landscape of preservative choices in pharmaceuticals. The preference for preservative-free or "clean label" products is driving pharmaceutical companies to explore alternative preservative options. Natural extracts and essential oils are gaining traction as they align with consumer preferences for safer and more sustainable options[36].

Clean Label Movement

The clean label movement, which advocates for transparency and simplicity in product ingredients, is influencing the pharmaceutical industry's approach to preservatives. Consumers are increasingly seeking products with familiar, natural ingredients and are wary of synthetic or chemical additives. As a result, pharmaceutical companies are under pressure to reformulate their products with preservatives that align with the clean label movement. Some examples of preservatives that may be preferred in the clean label movement include rosemary extract, vitamin E, and grapefruit seed extract[37].

Demand for Minimalistic Formulations

Consumers are showing a growing preference for minimalistic formulations that prioritize simplicity and safety. This trend is influencing the use of preservatives in pharmaceutical products, as consumers seek products with fewer and recognizable ingredients. Pharmaceutical companies are responding by exploring preservative systems that allow for minimalistic formulations without compromising product safety and stability.

As consumer trends continue to shape the landscape of preservative choices in the pharmaceutical industry, companies must remain agile in responding to evolving preferences while ensuring the safety and efficacy of their products. Embracing

these consumer-driven changes in preservative selection can position pharmaceutical companies for success in meeting the demands of the market[38].

Environmental Considerations of Pharmaceutical Preservative Disposal

It is essential for the pharmaceutical industry to address the environmental considerations of pharmaceutical preservative disposal. The disposal of pharmaceutical preservatives poses a potential risk to the environment if not managed properly. These preservatives can enter the ecosystem through wastewater discharge from pharmaceutical manufacturing facilities or through the disposal of unused or expired pharmaceutical products[39].

The consideration of environmental impact becomes crucial, especially for preservatives that may persist in the environment or have the potential to bioaccumulate. It is important to assess the environmental effects of pharmaceutical preservatives to prevent adverse impacts on aquatic life, soil quality, and overall ecosystem health[40].

Proper disposal and management strategies for pharmaceutical preservatives should be developed to minimize their environmental impact.

This may involve implementing specialized treatment processes to remove or neutralize preservatives before wastewater discharge, establishing protocols for the safe disposal of expired or unused pharmaceutical products, and promoting initiatives for the proper recycling or disposal of pharmaceutical packaging materials[41].

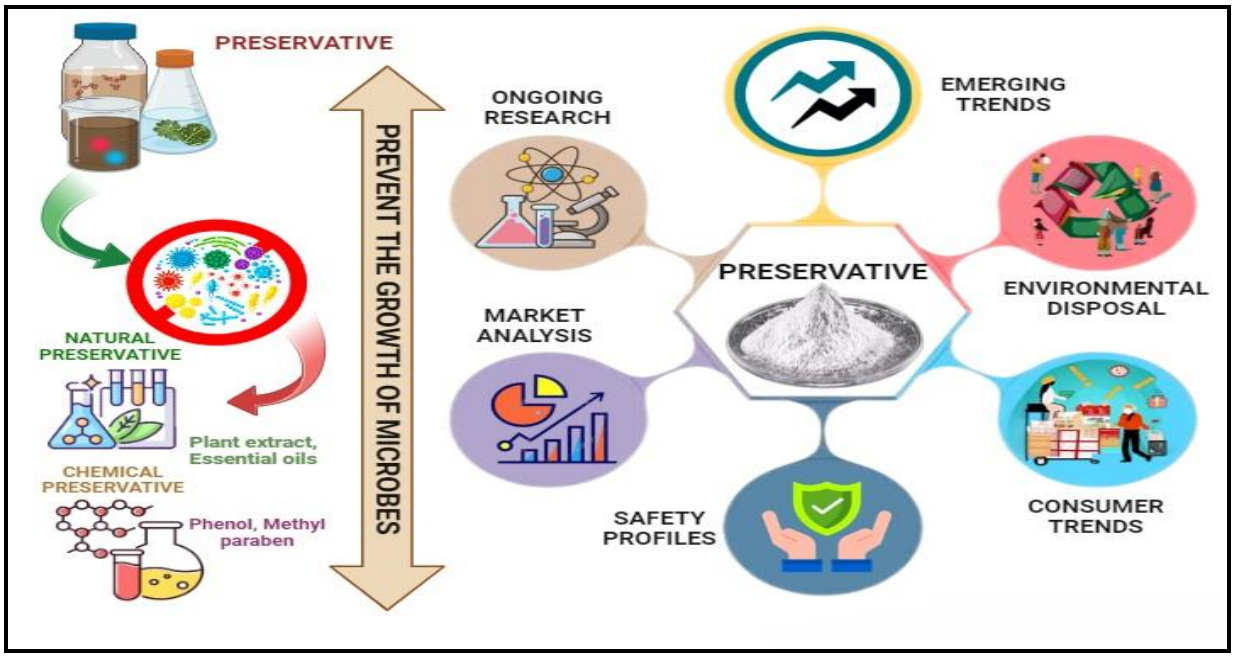
Furthermore, the pharmaceutical industry can explore sustainable and eco-friendly alternatives for preservatives to mitigate their environmental footprint. Research and development efforts can focus on identifying preservative solutions that have minimal environmental impact throughout their lifecycle, from production to disposal.

By acknowledging and addressing the environmental considerations of pharmaceutical preservative disposal, the pharmaceutical industry demonstrates its commitment to sustainability and environmental responsibility. Developing and adhering to proper disposal protocols and promoting the use of environmentally friendly preservative alternatives can contribute to the industry's efforts in minimizing its environmental footprint.

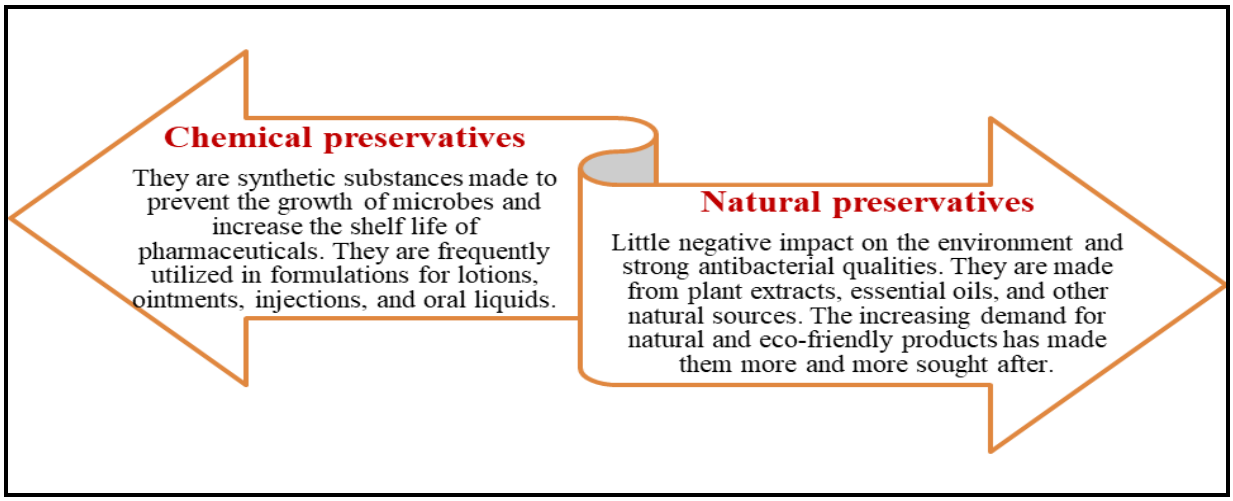
Table No.1: Some Common preservatives used in pharmaceutical preparations with their concentrations[22]

S.No	Preservative	Class	Concentration in Preparations (In %)			
			Oral Liquid	Parenteral	Ophthalmic/ Nasal	Ointments and creams
1	Methyl Paraben	Amino aryl acid esters	0.25	0.01-0.5	0.1	0.001-0.2
2	Ethyl Paraben		0.1-0.25	0.01-0.5	0.1	0.001-0.2
3	Propyl Paraben		0.5-0.25	0.005-0.02	0.1	0.001-0.2
4	Butyl Paraben		0.1-0.4	0.015	0.1	0.001-0.2
5	Benzyl Alcohol	Alkyl/ aryl alcohols	3.0	0.5-10	--	--
6	Chlorobutanol		0.5	0.25-0.5	0.5	0.5
7	Phenol	Phenols	0.1-0.5	0.065-0.02	--	0.25-0.5
8	Meta cresol		0.15-0.3	0.1-0.25	--	0.1-0.3
9	Chlorocresol		0.2	0.1-0.18	--	0.1-0.3
10	Benzoic acid	Alkyl/aryl acids	0.1-0.2	--	--	--
11	Sorbic acid		0.1-0.2	--	--	--
12	Thiomersal	Organic mercurials	0.1	0.01	0.01	0.01
13	Phenylmercuric nitrate		0.002-0.1	0.002	0.004	0.002
14	Bronopol	Diols	0.01-0.1	--	--	--
15	Propylene Glycol		15-30	--	--	--
16	Benzalkonium Chloride	Quaternary Ammonium Compounds	0.002-0.02	0.01	0.004-0.02	0.01
17	Benzethonium Chloride		0.01-0.02	0.01	0.004-0.01	0.01

GRAPHICAL ABSTRACT



VARIOUS PRESERVATIVES IN PHARMACEUTICAL PRODUCTS



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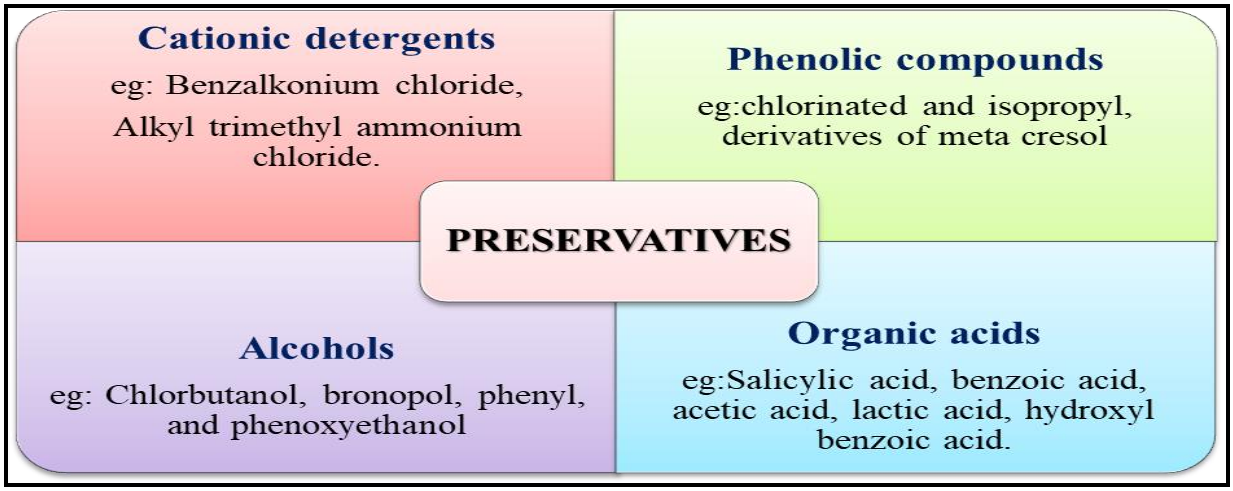

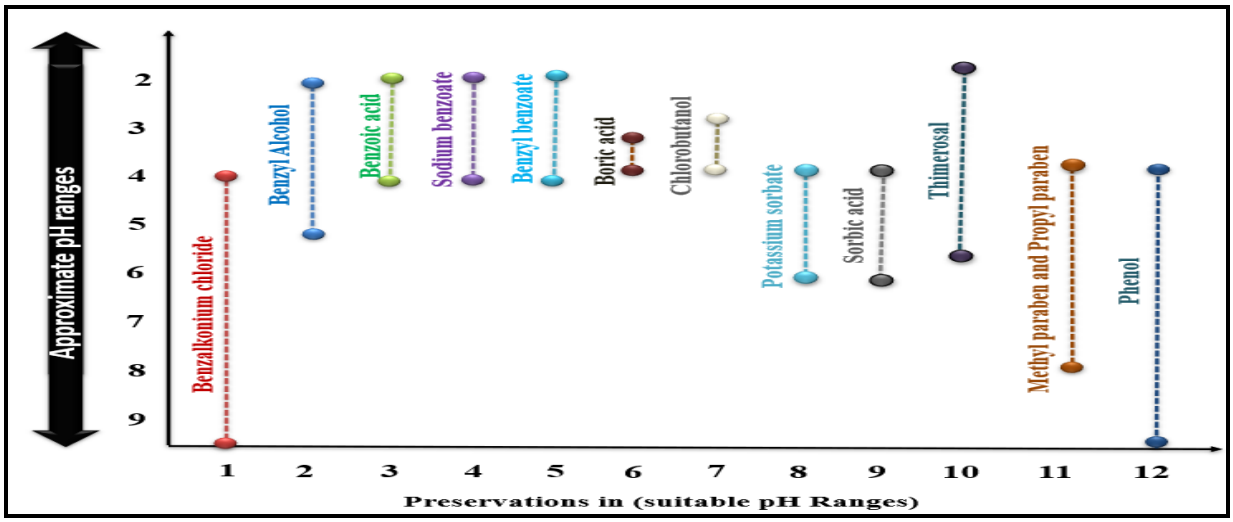

Figure No.1: Approximate pH ranges followed for preservatives

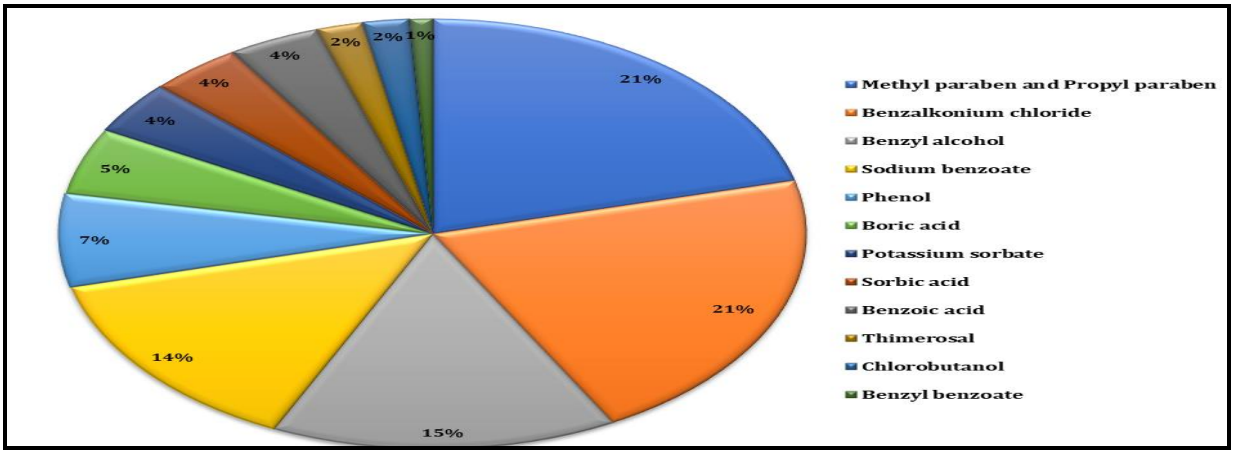

Figure No.2: Pie-chart represents the % concentration for various chemical and natural preservatives

CONCLUSION

In conclusion, the need for preservatives in pharmaceutical formulations is undeniable, as they play a crucial role in maintaining product safety and efficacy. Regulatory guidelines dictate the types and allowable concentrations of preservatives to ensure that pharmaceutical products meet safety standards and mitigate potential health risks for consumers. While the safety profiles of common pharmaceutical preservatives have been extensively studied, the industry is continuously exploring new, more sustainable options to align with consumer demand. The safety of pharmaceutical preservatives is a top priority, and it is essential for companies to adhere to regulatory guidelines and prioritize consumer safety. Moreover, the evolving consumer trends towards clean label products and minimalistic formulations are influencing the choice of preservatives in pharmaceuticals. Pharmaceutical companies must strike a balance between meeting consumer preferences and ensuring the safety and stability of their products.

Environmental considerations regarding the disposal of pharmaceutical preservatives are also paramount. Proper disposal and management strategies are necessary to minimize their environmental impact and prevent adverse effects on the ecosystem. The industry's commitment to exploring sustainable and eco-friendly alternatives for preservatives demonstrates its dedication to environmental responsibility.

While the pharmaceutical industry is navigating consumer trends and environmental considerations, the safety and efficacy of pharmaceutical products remain the cornerstone of preservative usage. This balance between consumer demand, safety, and environmental responsibility will continue to shape the landscape of pharmaceutical preservatives in the years to come.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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