A Short Overview of Benzalkonium Chloride in Pharmaceutical Sector: Safety, Environmental Impact and Alternatives

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Abstract

This paper provides an overview of the environmental and safety concerns associated with benzalkonium chloride (BAC), a chemical widely used in pharmaceuticals. The review covers BAC's various applications, toxicity, and environmental considerations. It explores the industrial processing of BAC, its role as a preservative in drug formulations, and the negative consequences linked to its usage. Furthermore, the review highlights the potential allergic reactions following the initial application of BAC. The study also refers to the various concentrations of BAC employed in different formulations and their administration for safety purposes. Additionally, initiatives to use alternatives to BAC in order to mitigate the potential side effects are explored.

Keywords: Benzalkonium chloride (BAC); disinfectants; antimicrobial preservatives; toxicity; environmental impacts; alternative substances

Introduction

In addition to being referred to as alkyl dimethyl benzyl ammonium chlorides, ammonium alkyl dimethyl (phenylmethyl) chlorides, and alkyl dimethyl (phenylmethyl) quaternary ammonium chlorides, benzalkonium chlorides (BACs) are also referred to as quaternary ammonium compounds (QACs), whose structure is illustrated in Figure 1. Due to their greater biocidal activity, C12 and C14 derivatives are usually sold in mixtures of compounds with chains from C8 to C18. This mixture is usually sold commercially [1]. Gerhard Domagk originally revealed BAC

in 1935. The first product in the United States to include BAC was registered with the Environmental Protection Agency (EPA) in 1947 [2].

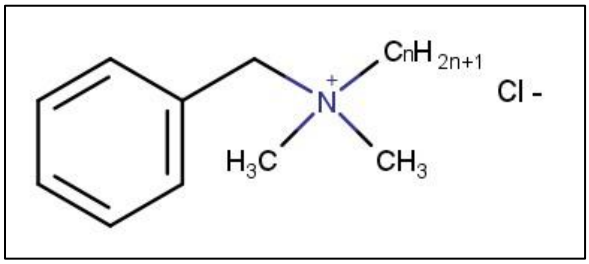

Figure 1. The chemical structure of benzalkonium chloride, where n =8, 10, 12, 14, 16, 18.

Because of their stability, high antibacterial activities in acid formulation, and long shelf life, the quaternary surfactants benzalkonium chloride (BAC) and benzathine chloride are selected by a significant number of producers. Benzalkonium chloride (BAC) can range from being colorless to having a very light-yellow hue, depending on its purity (impure). There is a high degree of solubility of benzalkonium chloride in both ethanol and acetone. Although dissolving in water for most of substances is a sluggish process, but BAC is highly soluble in water. In general, aqueous solutions are chosen because they are simpler to work with. It is recommended that aqueous solutions have a neutral to slightly alkaline pH [3]. In addition to being cationic surfactants, BAC is also frequently utilized as a disinfectant and germicide due to the powerful protein-denaturing effect that they possess. A solution of 10% BAC combination is typically utilized, particularly in hospitals; this solution is then diluted to a solution that is between 0.05 and 0.1 % with the intention of being used for a variety of disinfection procedures [4, 5].

Although BAC is most employed as a preservative in eye drops, it is also utilized as an antiseptic and disinfection when it is present in higher quantities. Two amounts of BAC, 0.1% and 0.4%, were tested that utilized for this purpose [1].

In veterinary medicine, an injectable glucocorticoid formulation that is intended for use in cattle, pigs, horses, sheep, goats, and pigs contains BAC as an excipient is utilized. The concentration in this formulation is less than 0.05%, which results in a dose that is approximately between 0.006 and 0.009 mg/kg body weight [6].

As soon as it is used for the first time in drugs, there is a possibility that BAC might cause allergic responses such as a rash, itching, hives, swelling of the face, lips, or tongue, chemical burn, or skin irritation such as redness, burning, or stinging that does not go away, as well as a mild tingling

feeling [7, 8]. These allergic symptoms might also appear in post oral ingestion alterations in tongue, pharynx, larynx, esophagus, and stomach that may have been exposed to BAC. BAC-exposed digestive tract and surrounding regions revealed erosion but no inflammatory cell infiltration. Acute kidney tubular necrosis and liver central lobular necrosis were compatible with acute circulatory failure [9, 10].

The aim of the research is to find answers to questions like, Is the proof of the toxicity of BAC substances in medicine sufficient? Have earlier studies confirmed that or have they failed to do so? What are the most harmful exposures to this chemical when taking it medicinally, and what are the effects, if any, that were observed on humans? Evidence supports the impact of the medicine on the environment after consumption, particularly in used waters [11].

Benzalkonium Chloride Synthesis and Manufacturing Process

Benzalkonium salts are an economically important group of industrial chemicals that are used in a wide range of products and situations, from manufacturing to everyday life [11]. Benzalkonium chloride (BAC) syntheses require alkyl dimethyl amines, which are tertiary amines with two methyl groups and a third alkyl group, C8–C18 [12] and benzyl chloride, a white liquid with a pungent odor, induces eye tears [13]. Benzyl chloride primarily changes molecules' chemical characteristics by adding benzyl functionality. This is used to make plasticizers, sanitizers, oil extraction products, and medicines [14]. The known method for producing benzalkonium chloride (BAC) by interaction of tertiary amines with benzyl chloride is illustrated in Figure 2. Where R stands for the aliphatic hydrocarbon radicals that (alkyl radicals). A tertiary amine mixture is made up of amines with alkyl radicals. There are a lot of tertiary amines in the mixture that have alkyl radicals with more than 14 carbon atoms, which made the final product, alkyl dimethyl benzyl ammonium chlorides, benzalkonium chloride BAC, are toxic [15].

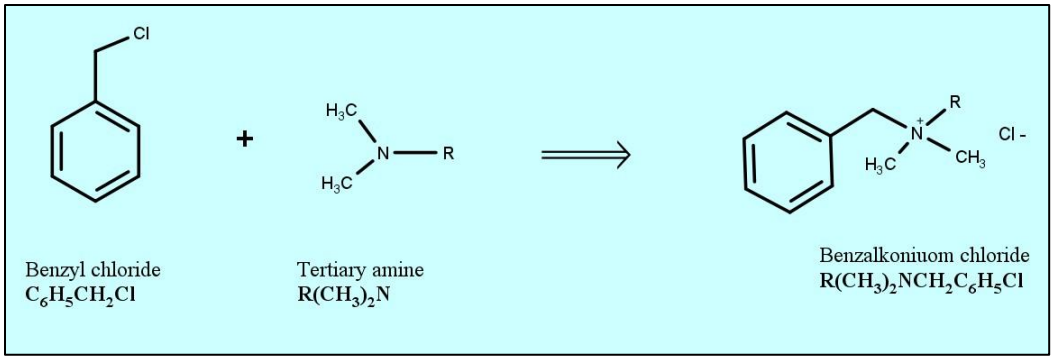

Figure 2. Preparation reaction of benzalkonium chloride.

Different rates of benzyl chloride's chemical reactions with tertiary amines and possible side results from substance interactions. This produces many impurities and undesirable alterations in the final product's valuable functioning properties. Refined tertiary amine dimethylcetylamine can be mixed with 0.5 mol of benzyl chloride at 78° C for 2–2.5 hours to make BAC with a final conversion rate of 92% [15].

BAC manufacturing comprises various industrial processes: The raw materials include alkyl dimethyl amine and benzyl chloride charging, along with a method for specification examination. The reaction stage involves the formation of benzalkonium chloride, the reaction requires applying heat to the reactor chamber. Testing: the process of testing the product to ensure its quality. Filtration step to remove any impurities. Packing is the final step in packaging the product for distribution.

The process uses toxic raw materials that could be harmful to people and the environment during the processing steps [16, 17]. Therefore, quality assurance is conducted through a testing phase to ensure the product meets specified standards [18]. This is followed by a filtration step designed to remove impurities, which can result in waste products that must be handled to prevent environmental contamination. The final step is the packaging of the BAC for distribution, during which care must be taken to avoid any spillage or leakage that could harm the environment. Considering environmental concerns is always essential when meeting the requirements for eco-friendly industrial processes [19].

Another method for preparation of BAC solution involves mixing di alkyl methylamine and benzyl chloride in alkylene glycol at 95–100°C and reaction time of 5 hours. The process takes too long and produces a quaternary ammonium compound solution that is not very strong [15].

Benzalkonium Chloride Uses in Drugs

Benzalkonium chloride (BAC) disinfects and preserves, it is in most multi-dose aqueous nasal, eye, and ear products. Preservative for eye drops, at 0.01-0.02%, it has been the most common eye drop preservative since the 1950s, its multidose container-effective bactericide and fungicide and reduces organism growth. Many drugs contain preservatives, ophthalmology's main preservative is BAC [20]. More than 200 EU-approved nasal and 10 inhaled medications contain BAC as a preservative. Some BAC medicines can be used on the skin, oral cavity, oral mucosa, rectal, vaginal, and parenteral routes [21].

Even though ocular medicines containing BAC might cause allergies and dry eye symptoms, BAC is used in approximately 70% of ophthalmic formulations in concentrations that vary between 0.005 and 0.2%. Even though ocular medicines containing BAC might cause allergies and dry eye symptoms, BAC is used in approximately 70% of ophthalmic formulations in concentrations that vary between 0.02 - 0.04% [22]. Side effects of this medication include eye pain, change in vision and clarity, redness, and eye irritation, hence it should be used with caution under the supervision of a doctor especially with cases of pregnancy and breastfeeding period [23]. BAC is effective against common ear pathogens like at concentrations between 0.004% and 0.01% [24]. However, high concentrations of BAC can build up in the lipid layers of the tear film and external auditory canal, which can damage them and make it harder for them to heal over time [25].

Refined BAC nasal drops relieve stuffy noses (blocked noses). The concentration of BAC in nasal sprays, drops, and ointments is usually ranges from 0.005% to 0.2%, other concentration might be used [26]. Moisturizes and loosens nasal mucus to relieve congestion quickly. Sodium chloride and benzalkonium chloride nasal drops moisturize the nose [27]. This helps treat a stuffy nose from a cold or allergies [22]. Using nasal decongestants for allergic rhinitis for a long time can cause "rebound swelling" and more congestion [28]. The preservative BAC in most decongestant sprays can worsen allergic rhinitis and cause toxic reactions in the nose, eyes, ears, and lungs [29]. Recently published studies show BAC nasal sprays' effects. A measure of nasal swelling and reactivity with histamine tests found that BAC induces swelling and hyperreactivity [30]. BAC 0.15% antiseptic gel is a semisolid dermatology product. Precise skin application targets the treatment area with this design. Patients allergic to any of its ingredients should not use this

antiseptic gel on open wounds, broken skin, eyes, ears, and mucous membranes due to potential harm [31].

The tear film and auditory canal could get damaged from BAC buildup in lipid layers. Using medications containing BAC with caution and medical supervision is essential due to the potential for toxic reactions and rebound swelling. This is particularly important during pregnancy and breastfeeding. Making educated and conscientious medication decisions requires knowledge of these risks.

Mechanism of Benzalkonium Chloride Toxicity

Toxic effects in humans caused by BAC and other quaternary ammonium compounds (QACs) are mainly associated with their chemical structure and mechanism of action. Benzalkonium chlorides interact with negatively charged components of bacterial cell membranes, such as phospholipids and lipopolysaccharides, because their nitrogen atoms are positively charged [32]. This interaction is the mechanism of action. Cell death occurs when this interaction compromises the integrity of the cell membrane, which allows cellular contents to seep out [33].

The method of BAC action is good for disinfection, but it is harmful to humans because BAC damage bacterial cell membranes, which can induce toxicity in human cells at high doses or prolonged exposure [34]. Absorption of BAC through the skin, lungs, or gastrointestinal tract can cause systemic toxicity, affecting many organs and systems, this can harm the liver [35]. BAC vary in toxicity according on chemical, concentration, and exposure time. Avoiding health risks requires proper BAC handling, use, and disposal according to safety standards as mentioned before. BACs' capacity to interact with cellular components and break cell membranes is the primary mechanism by which they might cause hazardous consequences in humans. Toxic action mechanisms are described in further depth here. Because of their positively charged nitrogen atom, BAC can interact with phospholipids and proteins, which are negatively charged components of cell membranes [36]. As a result of this interaction, the following outcomes are possible: enhanced permeability of cell membranes; hence, bacteria can clench lipid bilayers, allowing enzymes, proteins, and electrolytes to flow out of cells, causing complete disintegration and cell lysis (rupture) [37]. Solubilizing lipids in the cell membrane, which results from BAC at greater concentrations, leads to essential cellular functions disruption when BAC bind to and block the activity of enzymes that are linked to the cell membrane [38].

BAC can also be harmful by denaturing proteins and inhibiting enzymes [39]. BAC alter protein tertiary and quaternary structures, denature enzymes, and interact with them. It can hinder critical enzymatic processes and disrupt cellular functions [40]. BAC poisoning may cause oxidative stress and mitochondrial malfunction [41]. BAC may deplete cellular antioxidant defenses, causing oxidative stress. Lipids, proteins, and DNA can be damaged by oxidative stress [42]. Energy production and cellular respiration are also hampered by BAC, which alter mitochondrial function. Genotoxicity and mutagenicity are other types of BAC toxicity that can cause DNA damage, chromosomal abnormalities, and mutations [43]. Cancer and other genetic problems may result from these impacts. Immunotoxicity, where BAC break cell membranes and impair immune cells like macrophages and lymphocytes from recognizing and responding to infections [44]. Neurotoxicity, BAC can cross the blood-brain barrier and disrupt neuronal cell membranes, change neurotransmitter release, and cause central nervous system oxidative stress [45].

The exact chemical, concentration, exposure method, and duration are some of the variables that determine the degree to which BACs are hazardous to the human body. Minimizing the danger of harmful health consequences requires following suitable safety rules and regulations when handling and utilizing BAC.

Characteristics of Potential Risks of Benzalkonium Chloride on Human Health and Environment

Benzalkonium Chloride (BAC) poisoning is the result of significant exposure to high concentrations of BAC. The poisoning can result from ingesting, inhalation, or cutaneous contact. The toxicity threshold of blood concentration of BAC might fluctuate based on the length of exposure and method of ingestion. The recognized fatal dose for humans ranges from 50 to 500 mg/kg, depending on the concentration of BAC in the product and the mode of exposure [46, 47]. BAC poisoning can cause a variety of symptoms, including nausea, vomiting, and discomfort in the stomach. coughing, wheezing, and shortness of breath are all symptoms of respiratory problems. Lung damage, chronic respiratory problems, and even respiratory collapse are all potential outcomes of prolonged exposure to the substance. Blister formation, skin irritation, and redness are other symptoms might be generated [48, 49]. Sensitization of the skin and allergic reactions are possible outcomes of prolonged or repeated exposure to the substance. If the chemical is allowed to come into contact with the eyes, it may cause inflammation, redness, and irritation in

the eyes [50]. Itchiness, hives, swelling, and difficulty breathing are some of the symptoms that are associated with allergic reactions [7]. As a result of extreme circumstances, seizures, tremors, and loss of consciousness are all possible outcomes [51].

BAC also impacts the digestive system. Studies have shown that exposure to small amounts of these antimicrobial substances, particularly BAC, can lead to an increase in colitis. Furthermore, exposure to BAC was discovered to enhance Toll-like receptor 4 (TLR4) signaling in the systemic circulation by affecting intestinal barrier function, leading to increased amounts of bacterial products in the bloodstream. These findings indicate that commonly used antimicrobial agents may exacerbate the progression of inflammatory bowel disease and its related colon cancer [52].

Therefore, it is important to note that BAC poisoning is highly hazardous and can occur due to significant exposure levels through ingesting, inhalation, or skin contact. Fatal dosages vary from 50 to 500 mg/kg, depending on the level of exposure. Symptoms may manifest as gastrointestinal disturbances, respiratory troubles, dermatitis, and ocular inflammation, with severe instances resulting in seizures and loss of consciousness. BAC exacerbates colitis and may promote colon cancer by impacting the digestive system. BAC presents immediate and long-term health hazards, requiring carefulness and preventive actions.

Pharmaceutical manufacturing facilities, especially those dealing with very hazardous compounds, present substantial environmental hazards [53]. The hazards arise from different phases of production, such as raw material handling, synthesis, purification, and waste disposal. Unintentional spills or leaks of harmful substances can pollute land, water bodies, and the atmosphere, causing significant ecological harm [54]. Insufficient treatment of wastewater with dangerous compounds can lead to prolonged contamination [55], impacting marine life and posing a risk to human health by accumulating in the food chain. Moreover, the release of toxic particulate matter in manufacturing operations adds to air pollution, worsening respiratory problems and climate change. Stringent rules and sustainable procedures are necessary to reduce the negative environmental effects of pharmaceutical manufacturing activities [56].

Pharmaceutical manufacturing and usage of BAC pose environmental risks. Mishandling or spills of BAC during manufacture can pollute soil and streams, harming local ecosystems [57]. In addition, inappropriate disposal of production facility waste containing BAC can cause long-term contamination that harms wildlife and humans [58]. After human use and excretion, BAC might enter wastewater systems. Insufficient wastewater treatment may discharge these substances into

natural waterways. Disrupting aquatic habitats can harm fish and other organisms [59]. BAC in wastewater can also generate more hazardous metabolites, endangering the environment [60]. Therefore, stringent regulation and adequate wastewater treatment are needed to reduce the environmental risks of BAC in pharmaceutical manufacturing and use. The risk may proceed when the BAC traces reach drinking water sources, making the purification process more complicated for drinking water treatment plants [61, 62].

Wastewater containing BAC can have significant impacts on the environment due to several factors. First, BAC is known to be persistent in aquatic environments, meaning they do not easily break down and can accumulate over time [63]. This persistence can lead to long-term exposure of aquatic organisms to these compounds, potentially affecting their health and reproductive capabilities. Additionally, BAC has been shown to have toxic effects on various aquatic organisms, including fish, algae, and invertebrates. Exposure to BAC can disrupt hormone regulation, impair immune function, and even lead to mortality in sensitive species[64].

Moreover, BAC can undergo transformation in the environment, forming potentially more toxic byproducts. For example, in the presence of sunlight and other organic matter, BAC can react to produce disinfection byproducts (DBPs) such as chlorinated compounds, which are known to be harmful to aquatic life and can also pose risks to human health when present in drinking water sources [65].

BAC in wastewater can also cause bacteria to become antibiotic-resistant. Antimicrobial drugs like BAC are released into wastewater, which can select antibiotic-resistant microorganisms. Antibiotic-resistant bacteria can make treating human and animal diseases difficult, which can affect public health [66].

BAC-containing wastewater can disrupt aquatic habitats by poisoning organisms, forming hazardous byproducts, and promoting antibiotic resistance. Thus, adequate wastewater treatment is necessary to reduce the environmental consequences of BAC in pharmaceutical effluent.

Initiatives to Reduce Toxicological Harm by Making Use of Non-Conventional Substances

Concerns about the safety and environmental impact of common substances, such as BAC, used in the pharmaceutical business are growing. As a result, there is a shift in focus toward researching non-conventional substances and strategies. Companies are making this change because they want

to lessen the bad effects of standard pharmaceutical compounds like heavy metals and synthetic chemicals. Right now, the most important goal of pharmaceutical research and development is to find ways to reduce toxicological harm by using rare chemicals. By using natural compounds, biodegradable materials, and new formulations, these projects want to make pharmaceutical products safer and help make drug production more environmentally friendly. This initiative looks at the growing trend of using non-traditional substances in the pharmaceutical business as a proactive way to deal with toxicological issues.

Quaternary ammonium compounds like benzalkonium chloride, 2-poly(ethyl alcohol), chloro-butanol, and parabens are typical preservatives that meet most of the antimicrobial required criteria. As stated Gupta, Mishra [67] in their study that preservatives in ocular formulations harm the epithelium, yet they are important in multi-dose containers. Since BAC causes ocular cytotoxicity, Polyquaternium-1, sodium perborate, and stabilized oxy chloro-complex are being investigated. For individuals with severe allergies or surgical circumstances, a preservative-free single-dose bottle was employed. Preservative-free containers must be sanitized and stored properly to prevent microbial growth.

Regarding some case studies in this context, in their 2017 study, Lee et al. [68] noted that concerned companies began reducing stabilizers while maintaining the medications from breaking down as soon as it was established that BAC was hazardous for patients' eyes since it can damage the lens and make the eyes dry. It has been thought of as BAC alternatives and produced non-preservative packs. An example of a hormone-like chemical is prostaglandin, which might alter the color of the lens and the skin around the eye. Despite these negative effects, it affects inflammation and pain in several ways. Researchers administered BAC-containing and non-preservative disposable packs of the drug (Tafluprost) to study participants and examined the impact of the 0.0015% dose on both products. To lessen the likelihood of unwanted side effects, many ophthalmologists are interested in prescribing prostaglandin analogs, which are both efficacious and non-preservative.

Referring to other case studies on this matter. Calvo-Flores and Mingorance-Sánchez [69] conducted research in 2021 on deep eutectic solvents (DES), which has inherent antibacterial properties that can eliminate microorganisms. Utilizing DES as biocides in various material compositions containing capric and lauric acids can eradicate certain gram-positive bacteria. Due to these characteristics, DES appears to be a promising option for managing and averting

infections. Another option proposed is the creation of an antibacterial deep eutectic by combining BAC with acrylic acid (AA). This compound can be incorporated into dental resin composites to provide long-lasting antibacterial materials that are biocompatible.

Ali and Lehmussaari [70] demonstrated that particulate polymeric delivery systems, such as microspheres and nanoparticles, can effectively transport pharmaceuticals while avoiding harmful effects. These systems differ in size. A microsphere is a particle larger than 1 μm, while a nanoparticle is a particle smaller than 1 μm. This separation is advantageous due to their distinct molecular and physical properties. No sterile eye products based on these technologies are currently available, but they show great potential in the field of ophthalmology, particularly for delivering medications to the retinal space at the back of the eye.

Future Prospective Based on the Current Study

Many ideas can emerge with respect to the potential outcomes of this study in the future. Examining novel molecules and methods to lessen the negative effects on human health and the environment caused by commonly used pharmaceuticals, such as BAC. Investigating novel formulations, biodegradable polymers, and natural substances with the goal of creating safer and more eco-friendly pharmaceuticals. The toxicological consequences of BAC, including its effects on human cells and organs, as well as the variables that affect its toxicity, such chemical composition, concentration, and exposure period, will require additional research. Research on the use of deep eutectic solvents (DES) in place of BAC, using these solvents for the elimination of microbes, and their intrinsic antibacterial characteristics. The ongoing investigation focuses on the potential dangers of BAC in various pharmacological forms, particularly those intended for the skin, eyes, and nose. Analyzing the possibility of BAC systemic toxicity through skin, lung, or gastrointestinal tract absorption.

Conclusions

There are major safety concerns regarding the possible toxicity of benzalkonium chloride (BAC), even though it is widely used as a preservative in medicinal materials. Variables such as the period of exposure, the mode of ingestion, and the concentration of the product all play a role in determining the threshold for toxicity. BAC poisoning poses a variety of risks, depending on these

variables along BAC journey from manufacturing to disposal in wastewater routes. These risks can be incurred through ingestion, inhalation, or cutaneous contact. To mitigate potential health risks, it is crucial to strictly adhere to strict safety standards when handling and applying BAC. However, to address the environmental and safety concerns associated with the use of BAC, there is an urgent need for extensive research into alternative chemicals and procedures. The investigation of natural substances, biodegradable materials, and new formulations is a promising route that can be pursued in order to improve the safety of pharmaceuticals and preserve the environment. Moreover, the disposal of BAC in wastewater presents an additional environmental risk, necessitating careful consideration and mitigation strategies to prevent adverse impacts on aquatic ecosystems and human health.

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