

ANTIBACTERIAL MATERIALS - A FUTURE INSIGHT

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Abstract: *In a XXI century marked by dynamism, with a population continuously rising, concentrated in high densities around large metropolitan areas and with a high migration potential from one continent to another, the possibility of an epidemic outburst due to pathogenic germs represents a real threat to human health. For this reason there is an increasing demand for manufacturing and using antibacterial materials. Problems due to traditional antibacterial materials arise due to their non-biodegradability, which directly affects the environment. The present paper represents an overview of benefits and disadvantages of antimicrobial materials, so as the solution that is better fitted to the needs of the modern society to be promoted.*

Key words: *antimicrobial materials, germs, bio-active, bio-passive.*

1. Introduction

Contact with pathogenic microorganisms is very hard to avoid, because of their microscopic size and overall widespread occurrence in the environment. Not long ago, the epidemic outbursts provoked by pathogenic microorganisms have severely affected humankind. Once synthetic antibiotics have been obtained, epidemic outbursts have been drastically reduced or even eradicated, but still the infections produced by pathogenic microorganisms continue to represent serious concern with doctors and biologists being more preoccupied due to the fact that bacteria are starting to develop resistance to common antibiotics. Lately, a large number of briefings [12] have been issued to the overall population on the fact that antibiotics should be used for short treatment periods at the recommendation of a specialist.

Furthermore, the soil and water have become in the last decades extremely contaminated due to excessive utilization of antibiotics [17], which in turn has led to the destruction of the natural microbial flora, responsible for many important environment processes. Significant investments have been made to prevent hospital infections. Health associations around the world are confronting with serious problems in treating *Staphilococcus aureus* infections, which could turn out to be fatal to the patients, or *Pseudomonas aeruginosa*, whose resistance to antibiotics has increased dramatically.

Microbiological contamination has been a concern also for NASA employees, due to the rapid development in the space programs and sending humans into orbit. They have developed several defense procedures against pathogenic germs, which are nowadays adapted and implemented by all the producers in the

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alimentary industry, which is commonly known as HACCP (Hazard Analysis & Critical Control Points).

Under these conditions, antimicrobial materials have imposed themselves as a preventive measure in the fight against pathogenic germs. The research conducted to date have proposed the utilization of antimicrobial materials in different domains: health (medical instruments, surgery rooms) [11], microbiology laboratory instruments [18], dental implants [2], as well as in open public spaces (public transportation, toilets), food industry (packaging, edible antimicrobial membranes, recipients) [7], [16] and in textile industry for the elimination of unpleasant odorous, preventing skin diseases and reducing fibers degradation [13] by using silver, zinc and trichlosan as antimicrobial agents.

In USA the efficiency of textile materials with antimicrobial agents as additives has been proved by AATCC (American Association of Textile Chemists and Colorists) and NSF (National Sanitation Foundation) [14]. As antimicrobial agents for textiles, recently phytochemicals (plant-derived substances) have been proposed [1], for example, Aloe Vera has been proposed as antimicrobial agent for cotton fabrics [6].

Other domains in which antibacterial materials are imposed are represented by the aeronautical domain and water distribution systems, where the necessity of such an antimicrobial material has been proven by research studies whose results have indicated the microbiological contamination of potable water as a function of plumbing material type [15]. The stagnation of water in domestic plumbing systems, at ambient temperature, automatically favours the proliferation of microbial flora. For this reason the emptying of stagnant water from domestic plumbing is recommended before use, but

such a large amount of water elimination implies high costs, which is inefficient for the average consumer. On the other hand, scientists draw attention on the fact that water must be consumed in a rational fashion, due to the continuous depletion of available water resources, due to climatic changes produced by pollution, it is estimated that, by the year 2020 water will represent one of the most sophisticated products. By using plumbing made from antimicrobial materials these shortcomings could be eliminated, especially because the etiology of pathologic infections produced by contaminated water is relatively well known and studied, even before the discovery of the pathogenic agents themselves. As a consequence, the dysentery epidemic from Detroit, U.S.A. that lead to over 50,000 infections is well known and documented.

2. What are Antibacterial Materials?

Antibacterial materials represent small-molecular or macromolecular organic or inorganic compounds that are able to eliminate bacterial contamination by two known mechanisms (Figure 1): bacteria removal or bacteria destruction. As a function of microbiologic contamination elimination mechanism, antibacterial materials can be classified as bio-active and bio-passive materials [3].

Bio-passive materials prevent the bacterial adhesion by ensuring a minimal amount of adsorbed proteins, effect that is obtained by hydrophilic films coverage. These hydrophilic films are able to form an interfacial layer that prevents the contact between the surface of the material and bacteria.

The disadvantage of these materials is that defect-free covering of the material with hydrophilic films is difficult. Potential coverage defects may lead to microbiological contamination.

Bioactive materials are divided into two main categories: biocide-releasing materials and contact-active materials. The first category of materials kills bacteria via the release of a low molecular-weight biocide and the second category achieves long-term storage of antimicrobial agents and is able to slowly release those active agents into the environment.

Some coatings attempt to overcome the issue of bio fouling by incorporating the active moiety into a bio-passive background, providing the surface with both bio-passive and bioactive activity. Dual functional bio-passive and bioactive coatings have been prepared, as example, via co-polymerization of 2-(2-methoxy ethoxy) ethyl methacrylate and hydroxyl-terminated oligo (ethylene glycol) methacrylate, to generate reactive hydroxyl groups, which allow the immobilization of Magainin I, a natural antimicrobial peptide [3].

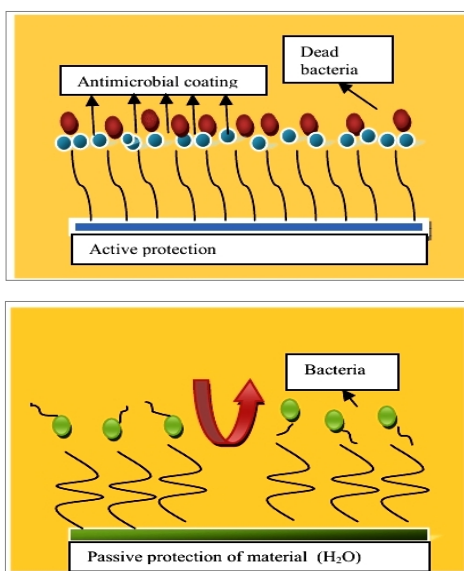


Fig. 1. *Bio-passive and bioactive material*

Polymeric antimicrobial materials have been intensively studied and promoted in the last decade. Polymeric materials are suitable matrices for antimicrobial agents or can themselves become antimicrobials

by chemical modification (grafting of ionic groups). One classification of antimicrobial polymers has been realized by Munoz-Bonilla: (a) polymers that exhibit antimicrobial activity by themselves; (b) those whose biocide activity is conferred through their chemical modification; (c) those that incorporate antimicrobial organic compounds with either low or high molecular weight; and (d) those that involve the addition of active inorganic systems [10].

3. Germs Multiplication Mechanisms on the Surface of the Materials

In order to efficiently assess the elimination of bacteria from the surfaces of interest, the mechanism of their multiplication must be understood.

Bacteria are prokaryotic cells that possess a very high capacity of synthesis and multiplication. They are able to asexually multiply by direct cell division at very high rates. Bacteria growth represents the biologic process through which they are able to increase their volume due to the synthesis of new compounds and water accumulation. Their growth is dependent on the surface/volume ratio, and continues as long as this ratio is greater than one.

When the surface/volume ratio becomes sub-unitary, the growing stops and the multiplication begins. Multiplication represents the increasing in the number of active germs in favorable conditions. This process is assessed as mentioned earlier by cell division. The division rate is very fast, usually 10-20 minutes under favorable environment conditions (an exception to this rule is the Koch bacillus, for which the multiplication period is 18-20 hours).

The multiplied bacteria attached to the surface of the material form a very hard to remove biofilm, whose role is to ensure bacterial adhesion and survival in difficult environmental conditions.

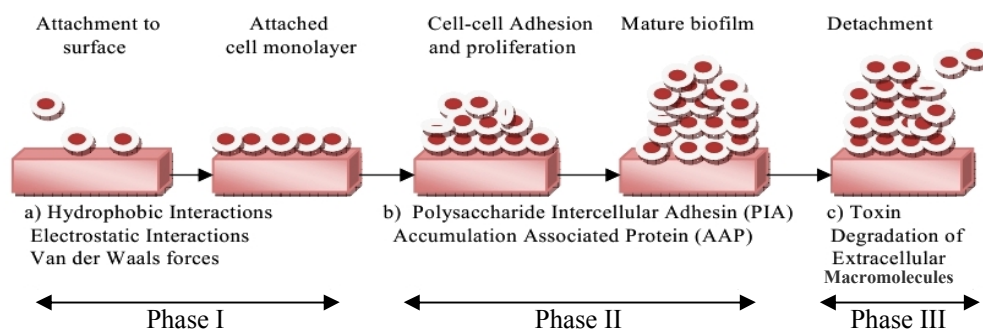


Fig. 2. *Biofilm formation mechanism*

Bacteria can switch between two distinct “forms of life”: a planktonic, free-living lifestyle (not attached to a surface) and a sessile state (forming communities). A biofilm is commonly defined as a structured complex community of one or more species of microorganisms. In contrast with free-floating, planktonic bacteria are 1000 times stronger to antibiotics action.

Bacterial adhesion to the surface of the material is realized in two phases: a) the initial physico-chemical interaction phase, determined by physical forces, such as Brownian movement, Van der Waals attraction forces, gravitational forces, electrostatic charges of the surface as well as hydrophobic interactions, and b) molecular and cellular phase. After biofilm maturation a third phase occurs, namely c) detaching of cells from the biofilm, as illustrated in Figure 2 [8].

4. Antimicrobial Activity Mechanisms

The antimicrobial activity is realized differently, as a function of the used biocide. Thus, as a function of the affected cellular organelles and the mechanism of action for different used antimicrobial agents, the following four classes of biocides are distinguished: a) Moderate Electrophiles; b) Extreme Electrophiles (Oxidants); c) Lytic Biocides; d) Protonophoric Biocides [9].

a) Moderate Electrophiles

In this category, most non-oxidant biocides could be included, such as isothiazolones. Their mechanism of action consists in their reaction with thiol groups from bacterial proteins and enzymes, releasing toxic free-radicals for the cell. Furthermore, isothiazolones can inhibit dehydrogenase enzymes in the respiratory pathways, affecting cellular metabolism. Respiration inhibiting leads to the cell's death in a few hours.

Bifunctional aldehydes (such as glutaraldehyde) contain two active aldehyde groups that can react with amino groups from proteins, cross-linking within and between proteins.

Other moderate metal-containing electrophile biocides (e.g. Fe, Ag) are able to specifically react with intracellular macromolecules, thus interfering with the cellular enzymatic activity.

b) Extreme Electrophiles (Oxidants)

The biocides from this category, for example chlorine, bromine, halogenated compounds are extremely reactive. The mechanism of action for these agents includes the halogenation of the macromolecules from the bacterial cell. Other oxidants can exist, which do not release active chlorine, such as chlorine dioxide, hydrogen peroxide, peracetic acid,

their mechanism of action consisting in generation of toxic free radicals inside the bacteria.

The oxidants are aggressive biocides, so as at moderate to high concentrations determine the functionalization of cellular membrane and the denaturation of specific cellular proteins or hetero-proteins. Also, non-specific binding to the nucleophilic functional groups bearing sulfur and nitrogen could occur, from critical cellular components, such as proteins, lipids, adenosine triphosphate (ATP), carbohydrates and nucleic acids.

Although these biocides are effective in metabolic disruption of the bacterial cell, their extreme reactive nature could also constitute a disadvantage. To penetrate inside the cell the oxidant must cross the outer layer composed of exopolysaccharides (EPS), the cellular wall and cytoplasmic membrane. The immediate reaction of the oxidant with these outer layers often leads to the formation of an impenetrable barrier consisting of oxidation reaction products, impeding the reaching of the oxidant to the inside of the cell.

c) Membrane Active - Lytic Biocides

The target of these biocides consists in the cellular membrane or the cytoplasmic membrane of the bacteria. Lytic biocides (e.g. quaternary ammonium compounds, polymeric quats, phosphonium quats, biguanides) mechanism of action consists in passing of the electrical-charged ions through the cellular wall, followed by their interaction with the cytoplasmic membrane. This interaction consists in the association to the negatively charged phospholipids, thus affecting the integrity of the membrane. Small concentrations of these biocides determine cellular breakdown, altering the bacteria metabolic functions.

d) Membrane Active Biocides-Protonophores

The biocides in this category also interact with the outer layer of the bacteria and are proton-conductors (e.g. parabens and weak acids, benzoic acid, citric acid, sorbic acid). It is to be mentioned that this type of biocides are active only against Gram-negative bacteria, at low pH. That's why the cellular wall polarity determination is extremely important when designing antibacterial agents.

The polarity of the cellular wall is different, as a function of its internal structure, which classifies bacteria in two main categories: Gram-positive and Gram-negative. The mechanism of action of protonophore biocides is represented by the ionic phenomena that occur at cellular-membrane level [3], based on the proton-motive disruption of cellular ATP metabolism. In this situation the bacteria could not produce a sufficient amount of energy to sustain its functions, thus using its own reserves. When these reserves are depleted, the bacteria die. The antimicrobial action of this type of biocides occurs very slowly in time.

5. Conclusions and Perspectives

Taking into account the large number of domains that manifest their interest for such materials, the great utility of such antimicrobial materials could be assessed. The major inconvenient of this type of materials is that they are non-biodegradable, which represents an important environmental issue.

A large number of synthetic polymers (without additives in composition) are themselves hard to biodegrade (within hundreds of years), without taking into account the antimicrobial ones. Due to this fact a lot of attention has been drawn by environmental-friendly polymers research,

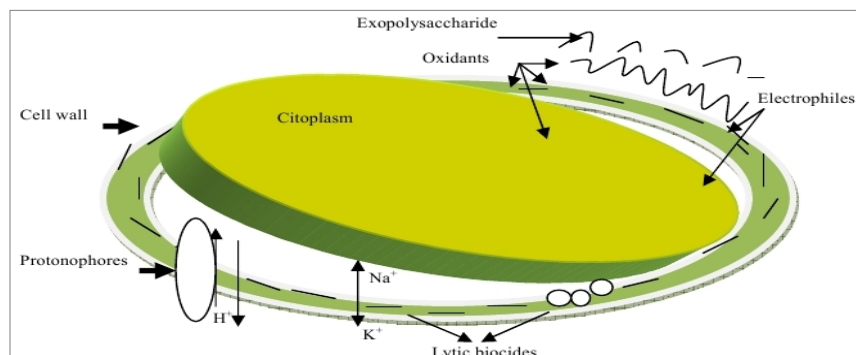


Fig. 3. *Adaptation after Luis F. Melo and Hans-Curt Flemming [9]*

the most promising one being chitosan, or other natural polymers with natural extracts as additives: nisin, essential oils (thymol, oregano oil, garlic oil), enzyme (lysozyme), antimicrobial peptides (AMPs) (Maganin 2, Histatin 5, Melittin).

On the other hand, antibiotics synthesis (antibacterial substances that function inside the organism) was a moment bearing maximum scientific importance, even if they pollute the environment in a higher amount than traditional antimicrobial polymers. Antibiotic substances are much harder to control and regulate and they generally present higher solubility and dispersibility, being discharged into sewage networks, polluting the water and soil, altering the natural processes that microorganisms are responsible with, which involves imbalances in the environment.

Trying to diminish the unwanted antibiotics effects, more and more "bio" alimentary products have been promoted in recent years, which are grown on carefully selected uncontaminated soils, but such products are expensive. Vegetables for baby-food production cultivated in contaminant-free soils have been the trend line of the last decade.

The benefits of antibiotics are widely recognized, still though their negative effects on the environment represent real threat concerns, so as lately, the prospectus of use for such medicine contains the

written warning to the overall consumer not to discharge in case of expiration, but to return to the pharmacy where it was originally bought.

By introducing antimicrobial materials in the critical points, the number of patients infected with pathogenic germs, as well as environment pollution could be greatly reduced, and moreover antibiotic resistance development could be avoided, taking into account the adaptation of the microorganisms and genetic mutations.

As with antibiotics, for antimicrobial materials the benefits/effects ratio ensures their recognition as positive achievements in raising health standards, environmental protection and conservation of microbial flora, so as the "good" bacteria, the main sanogenous agents of nature, responsible for the decomposition processes are protected.

Moreover, the antibacterial action takes place outside the body, which eliminates the side effects of medication, some people being exposed even to deadly risks when in anaphylactic shock. Also by ingesting antibiotics the natural microbial flora involved in digestion is destroyed.

The future trend of antimicrobial materials has been recently the subject of an opinion poll realized by the Omnexus members (Figure 4). The results have indicated that the antimicrobial materials represent a large domain of interest, due to their numerous utilizations.

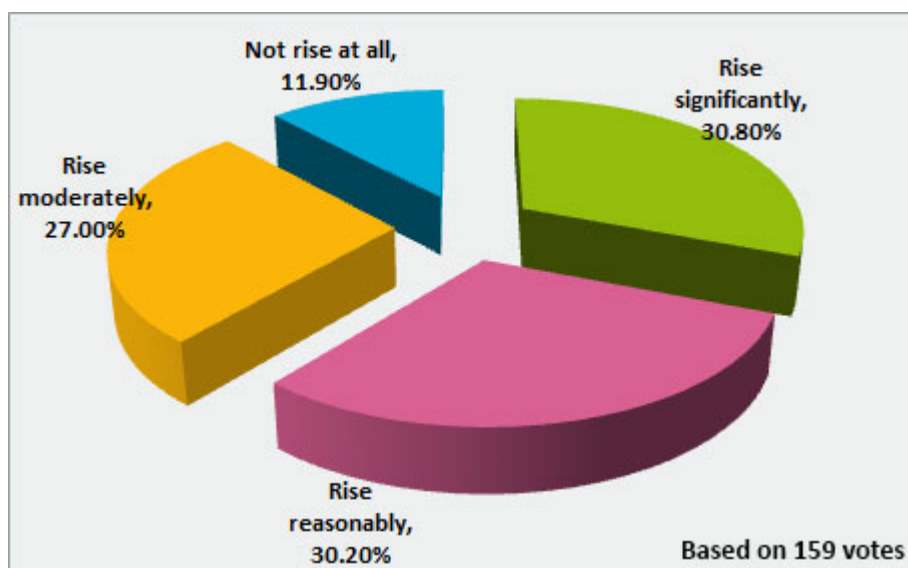


Fig. 4. *Bright future for antimicrobial materials gathered from Omnexus community results of the survey* [16]

Furthermore, HAIs (Healthcare Associated Infections) has emphasized the utilization of antimicrobial materials, due to the fact that the necessary funds for caring the patients affected by pathogenic infections could be considerably reduced [9]. Thus, the utilization of antimicrobial materials remains an open issue of great interest to the actual modern society [4], [5].

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