Preparation of medical devices with antimicrobial properties

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The present period is characterized by a strong growth of European interest in protecting life and the environment. Therefore a particular interest is given for product quality which does not endanger the life, health and safety of people and the environment. In this concept, the medical devices area represents a priority one which the main aim being the achieving a maximum efficiency for the patient as soon as possible, on the basis of knowledge of the physical, mental, family and socio-economic characteristics of the patient. This paper constitutes a mini-review of the most promising polymers and antimicrobial agents which can be employed to produce medical devices, the characteristics of some antimicrobial agents in order to give to polymers the antimicrobial features and set up the main requirements for the medical devices.

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1. Introduction

The present period is characterized by a strong growth of European interest in protecting life and the environment. Therefore a particular interest is given for product quality which does not endanger the life, health and safety of people and the environment.

In this concept, the medical devices area represents a priority one which the main aim being the achieving a maximum efficiency for the patient as soon as possible, on the basis of knowledge of the physical, mental, family and socio-economic characteristics of the patient.

Until now the medical devices have been used widely to save lives and the demand for these devices continuous to increase. There is also a clinical need for nonimplanted and shorter term usage of medical devices like catheters, drains, canulas, endotracheal tubes, etc.

Unfortunately, the widespread use of plastic medical devices could be followed by the infections with pathogenic microorganisms. Medical science has discovered that the infections that threaten patients treated with indwelling medical devices are caused by biofilm formation on the surfaces of the device**.**

Biofilms are microbial communities of microbes that are adhered to various surfaces and are engaged in a self-produced extracellular matrix and cause serious chronic infections. Infectious processes in biofilms are related to various routes such as urinary tract [1], catheter infections [1-3], formation of dental plaque [1], surgical site infections, ventilator-associated pneumonia.

In Fig. 1 it is shown a schematic representation of biofilm formation. Adherence of bacteria to a medical device surface is the first step in infection. Bacterial colonization of the surface leading to formation of a microbial biofilm has evolved as a natural growth and survival strategy for bacteria and is the preferred mode of existence in many areas over planktonic (suspension) populations. Rapidly dividing bacteria can spread along the surface of a device within the glycocalyx of the biofilm. After dispersion of the biofilm, bacteria move to other organs, tissues, or surfaces and a new biofilm is formed via stages **(**1**)–(**5). Bacteria within a biofilm can be 1,000 times more resistant to antibiotics than their planktonic counterparts.

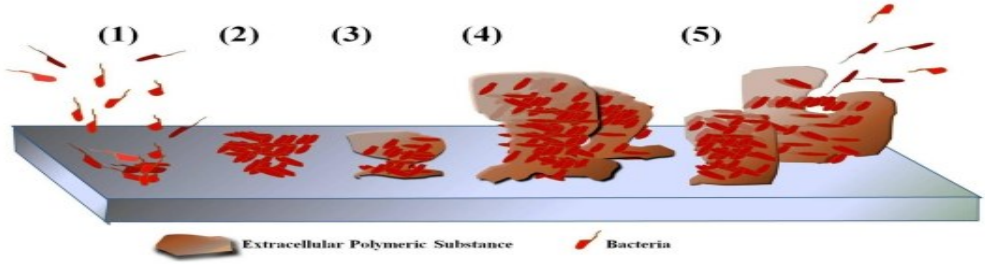

Fig. 1. General overview of bacterial biofilm development [1]
*(**1**) reversible adsorption of bacteria; (**2**) irreversible attachment of bacteria; (**3**) production of extracellular polymeric substance and biofilm growth; (**4**) maturation; (**5**) dispersion*

For instance, *Pseudomonas aeruginosa* bacterium is one of the most common causes of health care associated infections and is increasingly resistant to many antibiotics. *Pseudomonas aeruginosa* readily colonizes the surface of urinary catheters, forming adherent biofilms [4, 5].

Staphylococcus aureus is also a bacterium that commonly colonizes human skin and mucosa without causing severe problems [4].

Nosocomial pneumonia is one of the leading causes of morbidity and mortality in hospitalized patients [6]. During the past 20 years it has been reported that between 6 and 14% of patients that enter general hospitals develop a nosocomial infection [7], i.e., an infection that was not present or incubating at the moment of patient admission at a hospital.

The highest rate of infection is associated with urological catheters. The rate of infection is 5-7% per day for a catheter, so a patient using a urological catheter for a week would have a 35-39% chance of developing a catheter related infection [8].

Infections do not only occur upon the implantation of a medical device, but also during regular interventions. Postoperative infection associated with implants remains a serious complication in orthopedic surgery [9]. In patients with primary hip replacement, the infection rate during the first 2 years is usually less than 1%, and in those with knee replacement less than 2%. Infection rates after revision surgery are usually considerably higher (5–40%) than after primary replacement [10]. Overall, about 5% of internal fixation devices become infected [11]. Treatment of implant-associated infection requires appropriate surgical intervention combined with a prolonged antimicrobial therapy.

These infections result in prolonged hospitalization and are associated increased health care costs, but also in higher morbidity.

As a result, there is a continuous search to overcome or control such problems, which has resulted in antimicrobial medical devices. Term antimicrobial means "destroying or inhibiting the growth of microorganisms and especially pathogenic microorganisms".

In this sense, polymers due to their intrinsic properties are extensively and efficiently employed in medical fields. Therefore, the use of polymeric materials with antimicrobial properties gains an increasing interest from both academic and industrial point of view. The roles of antimicrobial agents on a surface of polymers are to restrict biofilm formation and to exhibit bactericidal activity, in order to lead the inhibition of microbial colonization directly on the surface itself [4]. In this case the characteristics of the polymer such as its hydrophilicity or its molecular weight have a great influence on the final antimicrobial activity concerning aspects from the rate of biocide release to even conferring synergistic activities.

A variety of different agents have been used to combat these infections, such as: gentamicin [12], rifampicin [13], sulfadiazine, chlorhexidine-sulfadiazine-triclosan, nitrofurazone [14] and nitrofuroxone [15]. Particularly problematic is the resistant microorganisms that rapid and easily mutate their genes, making difficult their elimination.

Therefore, the use of antimicrobial medical devices will help to mitigate, combat and/or eradicate these infections, which means an improvement in the state of well-being.

This paper constitutes a mini-review of the most used polymers for manufacturing of plastic medical devices, the characteristics of some antimicrobial agents in order to give to polymers the antimicrobial features and set up the main requirements addressed medical devices. Among the various polymers and antimicrobial agents which exist, we highlighted only the most used for plastic medical devices.

2. Plastics currently used to manufacture medical devices

The currently used plastic materials to manufacture medical devices include both synthetic polymers [poly(vinyl chloride), poly(vinyl alcohol), poly(methyl methacrylate), silicone, poly(carbonates), polyurethanes, etc.] and biopolymers [starch, cellulose, polyhydroxyalcanoates, poly(lactic acid), etc.].

From 1930 to the 1950s, poly(methyl methacrylate) (PMMA) was the most widely used polymer for biomaterials as its biocompatibility and versatility made it the material of choice when rigidity was required in a medical device. PMMA is still used nowadays for bone cement, intra-ocular lenses, etc. [16].

In the 1940s, polyvinyl chloride (PVC) and polydimethylsiloxane (silicone) became available. Still today, PVC is the most widely used polymer to produce a lot of products as: blood bags, medical tubing, body fluids collection and enteral feeding products. As a consequence, the availability of antimicrobial plasticized PVC is undoubtedly important for health care applications [17].

Silicone was the first implantable elastomer since the hydrocephalus shunt first implanted in 1955 [16]. The flexibility of silicone allowed the development of flexible-device components. There are known siliconized latex catheters that are commonly used for urinary catheterization. This biomaterial has shown marked cytotoxicity in various human cell cultures *in vitro* [5]. The effect of siliconized latex urinary catheters on the *in vitro* activity of amikacin, ceftazidime, ciprofloxacin, norfloxacin and meropenem against *Pseudomonas aeruginosa* was investigated by A. Pascual et al. [5]. They concluded that catheter material itself affected the *in vitro* activity of meropenem, and that the bactericidal activity of all antimicrobial agents against *Pseudomonas aeruginosa* present in biofilms on the surface of siliconized latex urinary catheters decreased dramatically, this effect being more pronounced with meropenem.

Then, numerous medical devices were developed such as vascular prostheses (PMMA, polyethylene tubing), blood-pump devices (avothane polyurethane/polydimethylsiloxane copolymer), intraaortic balloon pump (latex rubber on polyethylene catheter), synthetic vascular prosthesis (Vinyon N - polyvinyl

chloride polyacrylonitrile copolymer), bone-fixation implants (polyester urethane rigid foam), heart-lung machines as well as tissue adhesives (cyanoacrylates and hydrocolloids), occlusive wound dressings (polyethylene), dental restoratives (glycidyl dimethacrylates, bisphenol dimethacrylates, polyurethanes), hard contact lenses (PMMA), polyurethane implants for orthopaedic-fixation devices, prostheses, scaffolds or bioartificial organs [16].

Since the last decade, polycarbonates (PCs) have attracted increasing attention in pace with their significant applications in the medical field, owing to their unique combination of biodegradability and biocompatibility. Polycarbonates have been commonly used as integral components of engineered tissues, medical devices and drug delivery systems [18].

However, since the 1990s, increased attention has been paid to the use of natural polymers due to the following reasons: i) growing interest in reducing the environmental impact of synthetic polymers; (ii) finite petroleum resources; and (iii) the availability of natural resources that are renewable, low cost and full biodegradable. Biomaterials are now well established all over the world for a wide variety of medical applications because of their high specific properties compared to conventional plastic materials.

Starch is a homopolysaccharide made from α-D-glucose and consist of two components amylose and amylopectin [19-22]. The smaller of the two polysaccharides, amylose is a linear molecules comprising of (1-4) linked α-D glucopyranosyl units having a molecular weight of several hundreds of thousands. Amylose is water-soluble but gives an unstable solution. The larger of the two components, amylopectin, is highly branched with molecular weight of several hundreds of millions. This structure contains α-D- glucopyranosyl units linked mainly by (1-4) linkages (as amylose) but with greater proportion of (1-6) linkages, which gives a large, highly branched structure. Solution of amylopectin is relatively stable. Starch is a biodegradable polymer which degrades very fast with the help of enzyme, amylase present in human saliva and also by microorganisms. Starch degrades very fast to generate α-D glucose. Starch is a very good media for microorganism growth.

So far, there are known medical applications of starch as: drug delivery carriers in tissue engineering applications [23], excipient for controlled oral drug delivery [24, 25], bone replacement [26].

Poly(vinyl alcohol) (PVOH) is a water-soluble and biocompatible polymer, with excellent chemical and thermal stability. Applications of PVOH are limited by its hydrophilicity, but chemical cross-linking improves its stability in aqueous media.

Until now, have been studied the use of PVOH in medical applications as: membrane [27], wound healing systems [28, 29], release dosage forms [30-34], contact lens [35], tissue engineering scaffolds [36, 37], surgical sutures [38].

Also, starch/poly(vinyl alcohol) blends have been extensively studied in biomedical field [39, 40], as hydrogel dressing [41], drug delivery [42-44], new bioartificial materials [45].

Polyhydroxyalkanoates (PHAs) are polyesters of 3, 4, 5, and 6- hydroxyalkanoic acids obtained by microbial production. Some bacteria however produce them without being subjected to any kind of nutritional constraints, for example, *Alcaligenes latus*. Depending on the number of carbon atoms in the monomeric unit, PHAs are classified as short chain length PHAs, scl-PHAs, that contain 3–5 carbon atoms, for example poly(3-hydroxybutyrate), P(3HB), poly(4-hydroxybutyrate), P(4HB), and medium chain length PHAs, mcl-PHAs, that contain 6–14 carbon atoms, for example poly(3-hydroxyhexanoate), P(3HHx), and poly(3-hydroxyoctanoate), P(3HO). Also, depending on the kind of monomer present, PHAs can be a homopolymer containing only one type of hydroxyalkanoate as the monomer unit, e.g., P(3HB), P(3HHx), or a heteropolymer containing more than one kind of hydroxyalkanoate as monomer units, e.g., poly(3-hydroxybutyrate-co-3-hydroxyvalerate), P(3HB-co-3HV), poly(3-hydroxyhexanoate-co-3-hydroxyoctanoate), P(3HHx-co-3HO), and poly-3-hydroxybutyrate- co-3-hydroxyhexanoate, P(3HB-co-3HHx) [46]. PHAs can be used in various applications including: medical field, pharmaceutical, nonwovens, adhesives, films, additives for polymers.

Poly(lactic acid) (PLA) is a biodegradable, biocompatible and compostable polyester derived from renewable resources such as corn, potato, cane molasses and beet sugar. It has a bright future as an environmentally friendly thermoplastic [47].

PLA was introduced in the market for medical sutures around 1968, instead of PHBV was introduced much later, in 1983. It is a chiral polymer in which molecules containing asymmetric carbon atoms have a helical orientation.

PLA has promising applications in packaging, consumer goods, fibers and in biomedicine because of its excellent mechanical properties, transparency, compostability and bio-safety.

Polyurethanes (PUs) are a large family of polymeric materials with an enormous diversity of chemical compositions, mechanical properties, tissue-specific biocompatibility and biodegradability, with mechanical flexibility and moderate blood compatibility being their most prominent features. Because of their diversity of composition and mechanical properties, PUs are among the most extensively used synthetic polymers in biomedical applications, and remain one of the most popular groups of biomaterials applied to medical devices after half a century of use in the healthcare system [48].

Among those, synthetic polymers, already used for clinically established products (poly(lactic-co-glycolic acid) (PLGA) and poly(ε-caprolactone) (PCL) [49], polymers under current clinical investigation, such as polyphosphazenes, and natural polymers such as collagen [21], elastin, cellulose, dextran, fibrin and hyaluronic acid (HA) have been proposed [21, 45, 50, 51].

3. Antimicrobial agents used to manufacture medical devices

A variety of antimicrobial polymers have been considered in several comprehensive reviews during the past decade. The most studied antimicrobial agents are: chitosan, nisin, silver and curcumin.

Chitosan

Chitosan has been proved and regarded to be biodegradable, non-cytotoxic and having some interesting biological activities. Chitosan is the N-deacetylated derivative of chitin, one of the most abundant polysaccharides found in nature (Figure 2) [22, 52, 53].

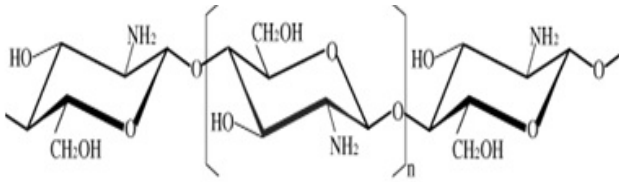

Fig. 2. Chemical structure of chitosan

Chitin is the second most abundant organic compound in nature after cellulose. Chitin, occurring as a structural polysaccharide in the outer skeleton of animals belonging to the phylum Arthropoda (animals walls of certain fungi and algae is quite abundant. It is also produced by a number of other living organisms in the lower plant and animal kingdoms, serving in many functions where reinforcement and strength are required [54, 55]. Chitin is insoluble in its native form but chitosan, the partly deacetylated form, is water soluble.

The potential of chitosan as a biomaterial is based on its cationic nature and high charge density in solution. In its crystalline form, chitosan is normally insoluble in aqueous solutions above pH 7; however, in dilute acids, the protonated free amino groups facilitate the solubility of the molecule which gives it the ability to chemically bind with negatively charged fats, lipids, cholesterol, metal ions, proteins, and macromolecules [56].

Chitin and chitosan have been used in many applications, mainly in the medical and pharmaceutical fields [55].

Kumari and Rani [56] reported blends of chitosan and starch for controlled release of drug.

According to John et al. [57] chitosan films (20 μm) showed no inhibitory effects against *Escherichia coli, Staphylococcus aureus* or *S. epidermidis* species. In contrast, solutions used to prepare the films showed almost complete inhibition (98 ± 2%) when tested on bacterial lawns and in liquid cultures. Increased acidity of the chitosan solutions (pH 5) was shown to promote the bactericidal effects of this biopolymer.

Chitosan and its derivatives are the antimicrobial natural polymers most used to confer their characteristics to non-active polymers. The most researches of Bonilla and Garcia [4] show that PU, PVP, PEO and PET were blended with chitosan and their efficiency tested against *E. coli*, *S. aureus* and *K. pneumonia* bacteria. The antimicrobial efficiency of chitosan was reduced only when the amount of PEO or PVP is 75% or 50%, respectively. Chitosan nanoparticles and quaternary ammonium chitosan derivative nanoparticles were also introduced in PMMA. The antibacterial activity was proved against *S. aureus* and *S. epidermidis*, where a 3-log reduction of 10^8 CFU/mL was found with a 15 wt% nanoparticles, and no cytotoxicity effect in mouse fibroblast is noticed.

Tomé et. al. [58] studied the antibacterial activity of thermoplastic starch-chitosan biocomposites against *S. aureus*. They found that biocomposites loaded with 7.5 wt. % the unmodified chitosan and of the quaternary ammonium chitosan derivative had partial and total bactericidal effects against *S. aureus*.

The major limitations in the use of the chitin and chitosan for designing medical devices are the collection of the raw material, difficult to obtain reproducible products with different raw materials, constantly high cost of production, the absence of validated process and products of biopolymer manufacture, no standardization of product quality and product assay methods for chitin and chitosan [53].

Nisin

Nisin is a polycyclic antibacterial peptide with 34 amino acid residues (Figure 3) [59].

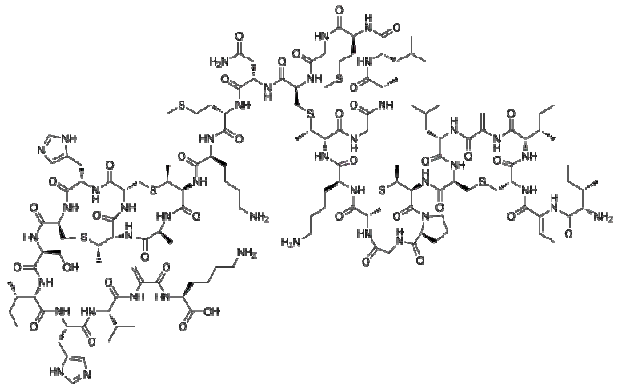

Fig. 3. Chemical structure of nisin

While most bacteriocins generally inhibit only closely related species, nisin is a rare example of a "broad-spectrum" bacteriocin effective against many Gram-positive organisms, including lactic acid bacteria (commonly associated with spoilage), *Listeria monocytogenes* (a known pathogen), *Staphylococcus aureus, Bacillus cereus, Clostridium botulinum*, etc. It is also particularly effective against spores. Gram-negative bacteria are protected by their outer membrane but may become susceptible to nisin action after a heat shock or when this is coupled with the chelator EDTA.

Nisin is soluble in water and can be effective at levels nearing the parts per billion ranges.

Due to its naturally selective spectrum of activity, it is employed as a food preservative and a selective agent in

microbiological media for the isolation of gram-negative bacteria, yeast, and moulds. In combination with miconazole it has been studied as a possible treatment for *Clostridium difficile* infections. Ongoing research seems to indicate that nisin may also have potential for slowing down the growth of certain tumors.

Tai et. al. [60] evaluated the antimicrobial activity of nisin-loaded, F108-coated polystyrene microspheres and F108-coated polyurethane catheter segments against the Gram-positive indicator strain, *P. pentosaceus.*

Also, the antimicrobial activity of nisin was demonstrated against *Broehothrix thermosphacta*, being stronger in the case of PE and PEO blends, followed by PE with EDTA [4].

Silver

Hippocrates, the "father of medicine", advocated the sprinkling of silver powder on ulcers to expedite healing, and silver has been used since World War I (and continues to be used) in wound dressings. Pencils or sticks of hardened silver nitrate (lunar caustic or lapis infernalis) were considered essential items in a surgeon's chest as early as the 1600s and silver nitrate solutions were used to treat burn victims of the Hindenberg disaster [61].

Though the use of silver as an antimicrobial temporarily fell out of favor after the proliferation of chemicals such as Penicillin, interest was revived in the 1960s and silver-based pharmaceuticals continue to be used today as topical and ophthalmic disinfectant.

Silver has numerous advantages over other antimicrobial agents. Compared to molecular antimicrobials, which are generally targeted to specific organism classes, silver is broad spectrum and toxic (to varying degrees) to numerous strains of bacteria, fungi, algae, and possibly some viruses [2, 61-66]. In addition, silver exhibits much higher toxicity to microorganisms than to mammalian cells.

The bactericidal activity of silver is dependent on the form in which it is applied. Metallic silver has been shown to possess only weak antimicrobial activity which deteriorates fast, and is strongly inhibited by protein adsorption to the silver. Silver in its metallic state can react with moisture to be ionized, releasing of highly reactive Ag^+ ions. These ions are highly potent as antimicrobial agent. Ionic silver is a single atom missing one orbital electron. The ionized silver can binds to proteins causing structural changes in the cell wall and also in the nuclear membranes provoking cell death. Ag^+ also forms complexes with bases contained in DNA and RNA inhibiting the microorganism replication.

However, almost all studied silver nanoparticles have very strong bactericidal activity. Furthermore several studies reported that the size and the shape of the silver nanoparticle influence the antimicrobial behavior, as well as its oxidation number, Ag^0 or Ag^+, in the matrix [2, 4]. Smaller sized silver nanoparticles (<10 nm) were demonstrated to have higher antibiotic activity than larger particles. However, the bactericidal mechanism remains to be understood.

Recently, Ando et. al. [67] investigated nanoparticles of silver and silver (I) oxide with great promise for widespread usage in medical polymers and nanodrugs. A possible explanation for the bactericidal activity of silver particles comprises the direct transfer of silver ions, from oxidized nanoparticles to biological targets as proteins or the cell membrane. This process is demonstrated in Figure 4.

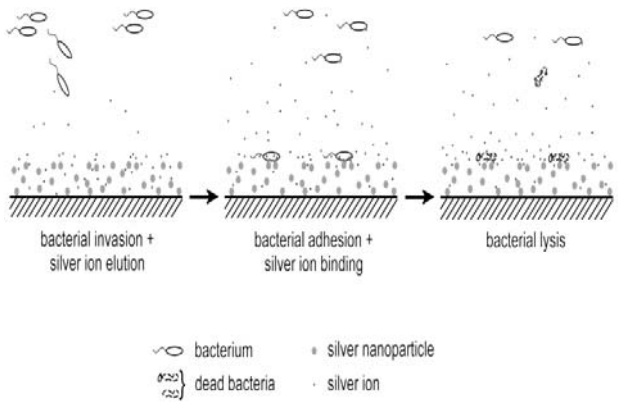

Fig. 4. Antibacterial mechanism of silver [67]

A surface coating containing silver nanoparticles will slowly release silver ions into the coating layer and subsequently the solution. Silver ions will bind the bacterial membrane and proteins, causing cell lysis. The silver ions can originate from the solution, but may also be transferred directly from the surface exposed silver to the bacteria without being dissolved in the medium [2].

One of the research paths was directed towards electrically injecting metal ions (silver) into solution by iontophoresis technique [6]. This has been shown to reduce bacterial colonization 15- to 100- fold in both bench-top and animal experiments. Bactericidal iontophoretic polymers can be designed to release silver ions when moistened with body fluids in the presence of silver and platinum powder. When the composite material is placed in contact with or immersed in an electrically conductive medium, such as saline, blood, or urine, or mucus, the metal powder becomes an array of small electrodes. Specifically, each metal granule embedded in the base material becomes either an anode or a cathode. Microbial growth is impaired through release of silver ions, with the generation of electric current from 1 to 400 μA.

The disadvantages of silver are related to its cost, silver ions are only available to release from surface or bulk that is accessed by moisture, negative effects on color and clarity of resin, relatively weak against fungi (yeast and mold) compared to bacteria.

Curcumin

Curcumin is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family (Zingiberaceae).

Curcumin is a low molecular-weight polyphenol, first chemically characterized in 1910, with the molecular formula of $C_{21}H_{20}O_6$ (Figure 5). The other two curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin. The curcuminoids are polyphenols and are responsible for the yellow color of turmeric. Curcumin can exist in at least two tautomeric forms, keto and enol. The enol form is more energetically stable in the solid phase and in solution.

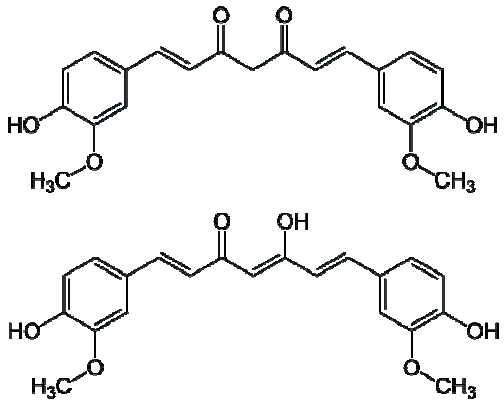

Fig. 5. Chemical structure of curcumin

In both *in vitro* and animal studies, curcumin has shown antitumor, antioxidant, antiarthritic, antiamyloid, anti-ischemic, and anti-inflammatory properties [68].

It is generally comprises 2–8% of most turmeric preparations. It has long been used as the yellow spice in Indian food and as a naturally occurring medicine for the treatment of inflammatory diseases [69].

The desirable preventive or putative therapeutic properties of curcumin have also been considered to be associated with its antioxidant property. Because free radical-mediated peroxidation of membrane lipids and oxidative damage of DNA and proteins are believed to be associated with a variety of chronic pathological complications such as cancer, atherosclerosis, neurodegenerative diseases, and aging, curcumin is thought to play a vital role against oxidative-stress-mediated pathological conditions.

Hence, the past few decades have witnessed intense research devoted to the antioxidant activity of curcumin. Before pointing out the potential antioxidant property of curcumin, it is worthwhile to outline the role of free radicals and antioxidants in health and disease.

4. Preparing of antimicrobial medical devices

There are known two approaches to incorporate antimicrobial agents into polymers: integrating into the device polymer or applied as a coating to the device surface.

Melt processing

Processing operations based on thermoplastic properties are used for the preparation of antimicrobial polymers on a large scale.

Normally, liquid suspensions or powder of silver nanoparticles are mixed with the molten polymer. As an example, nanocomposites of polyamide and polypropylene containing silver powder were produced by melt processing [4]. The Ag^+ release of the polyamide nanocomposites was higher than that of polypropylene, a more hydrophobic polymer. The polymer crystallinity also affects the release of Ag^+. These results can be explained by the water uptake; the highest Ag^+ release exhibited the highest water uptake among all the composites. In addition, there is a good agreement between the release of Ag^+ and the antimicrobial activity. Systems with low release potential showed excellent long-term antimicrobial behavior.

Another example is given by Zampino et al. [17]. Poly(vinyl chloride) (PVC) composites containing increasing amounts of silver zeolite (2–20%, w/w) were prepared by melt mixing and were characterized by thermal, mechanical and rheological analyses. The addition of large amount of silver zeolite did not influence the processability and the formability of the composites, if compared to neat plasticized PVC.

In another study, Damm and M□nstedt [62] have been reported nanocomposites based of PA6, PA6.6 and PA12-poly-THF filled with about 1.5 wt. % of silver nanoparticles that exhibit a good activity against *Escherichia coli.*

The advantages of this method consist in following:

- no additional manufacturing steps needed (cost savings),
- not affected by surface damage,
- prolonged release of antimicrobial agent.

This simple method has the disadvantage that residuals of the suspension liquid can remain in the polymer and direct incorporation of silver may negatively affect the properties of the device during manufacturing and/or use [62]. Silver is distributed throughout the polymer, but only the silver at the surface can be mobilized by moisture, the rest is unavailable.

The use of supercritical carbon dioxide is a promising technique for the impregnation of polymers with silver nanoparticles because no organic solvent is necessary [62].

Coating procedure

Coating procedure represents the most technique applied to a device to receive antimicrobial agents to provide device protection from infection.

Many studies have been reported relating manufacturing of silvercoated urinary catheters, cardiovascular implants, esophageal tubes, bandages, sutures and other instruments on which bacterial growth compromises patient survival [2, 61, 62, 67, 70].

The inclusion of silver nanoparticles, metallic silver, silver salts, or silver sulfadiazine in the coatings of medical devices all aim at releasing silver ions close to the surface. These ions can then reduce or even prevent colonization and subsequent biofilm formation on the surface. In this way the number of medical device associated infections can be reduced.

Coating the silver onto the outside surfaces of the device can be done by incorporating silver particles or silver salts into a coating which is ionically coupled or by plasma.

Silver sulfadiazine is widely and safely used in the clinical setting (catheters, urinary catheters, prostheses) [61]. The silver salt of sulfadiazine with or without chlorhexidine was developed recently. It is widely used to coat medical devices to prevent catheter-related infections and is currently the treatment of choice for burn wounds, as it has activity against gram-negative and gram-positive bacteria, fungi, protozoa, and certain viruses.

Berra et. al. [6] developed and tested *in vitro* several antibacterial-coated endotracheal tubes (ETT) using as antimicrobial agents: silver sulfadiazine in polyurethane, silver sulfadiazine and chlorhexidine in polyurethane, silver–platinum in polyurethane, chlorhexidine in polyurethane, and rose bengal for UV light. They prepared a dispersion of 53 g of silver sulfadiazine, and 22.5 g of polyurethane (BioSpan) in 210 ml of *N, N* dimethylacetamide. A standard 8-mm tracheal tube was inserted into a hollow transparent acrylic tube, to keep the ETT straight. With the plastic tube positioned vertically, the ETT tip was immersed into the dispersion, rapidly aspirated the dispersion up to the level of the connector piece, and then let the ETT drain for 2–4 s. Then the transparent plastic tube with the ETT was placed horizontally into a rotating device, through which a stream of air was gently passed to dry the dispersion. After 12 h, the coated ETT was removed and sterilized with ethylene oxide gas. It is found that in the *in vitro* study that silver sulfadiazine in polyurethane remained bacteria-free for up to 72 h.

The Ag+ release and, therefore, the antimicrobial activity were dependent on the silver nanoparticles content and on the deposition method. The spraying method forms tiny pores on the surface that enhance the biocidal activity toward *Pseudomonas oleovorans* bacterium and *A. niger* fungus.

As mentioned before, the size of the silver nanoparticle affects the activity, and efforts are being made to decrease its diameter. As an example, much smaller particle sizes, ≈7 nm, were prepared using invertible polyester and later, incorporated into thermoplastic PU [4].

Other antimicrobial medical device was prepared by using chitosan, as antimicrobial agent. A solution of chitosan was prepared by dissolving the biopolymer at 2% (w/v) in deionized water containing analytical grade acetic acid (2% v/v) and stirring for 6 h [71].

The advantages of coating procedure are related to:

- small quantity of material used,
- no effect on mechanical properties of bulk.

The drawback of coatings is that the surface properties of the device are changed. This can be a benefit, as it is in a lubricious silver coating added to a urological catheter. In most cases however, coatings alter surfaces negatively, including increasing dimensional thickness.

5. Requirements for antimicrobial medical devices

Medical devices field is covered by three directives that have established the design condition, technical and essential requirements to introduce on market: the Medical Devices Directive 93/42/EEC (MDD) (OJ L 169, 12.07.1993, as last amended); the Active Implantable Medical Device Directive 90/385/EEC (AIMDD) (OJ L 189, 20.07.1990, as last amended) (they were reviewed and amended by the Directive 2007/47/EC) and the Directive 98/79/EC on *in vitro* diagnostic medical.

Also, according to the FDA, medical devices that reduce or prevent device-related infections or reduce or inhibit microbial colonization on a medical device may be appropriate reasons to use an antimicrobial agent in a medical device [72].

For the design and evaluation of the performance of antimicrobial medical devices it is highly desirable to have a strong collaboration between material scientists, biologists and clinicians. Manufacturer of antimicrobial medical devices shall designed devices that are appropriate and address the intended use of the device, including the needs of the user and patient.

The most important requirements are concerning: the selection of the type and the rate of release of the antimicrobial agent, easy application, functionality, biocompatibility, sterility, animal and clinical tests.

Ideally, the selected antimicrobial agent should possess a lasting broad-spectrum antimicrobial activity and a low degree of bacterial resistance. In most cases, FDA requires high bacterial burden on surfaces (ex. 10^6 bacterial count) and high level of reduction (ex. 4-log). Depending on the application and duration requirements, studies show that depositing from 1μg/cm^2 to 32 μg/cm^2 of silver on medical device surfaces can prevent biofilm formation across a broad spectrum of pathogens including *Staphylococcus aureus, E coli, Pseudomonas aeruginosa, Enterococcus sp*, and *Candida albicans* [73].

The efficacy against the targeted microorganisms must be demonstrated after both 24 hours and 96 hours. Bonilla and Garcia [4] investigated the antibactericidal activity of silver/polyamide 6,6 nanocomposite by the log reduction test with *S. aureus* and *P. aeruginosa.* They showed that the four-level (10^4- fold) bacterial number drops after 18 h.

In other studies, the antimicrobial activity of a silver-impregnated polymer catheter (the Erlanger silver catheter) was demonstrated by determining the microbial adhesion to the surface of the catheter and by measuring the rate of proliferation (viability) of microorganisms at this site. On the surface of a catheter impregnated with silver, the bacterial adhesion of *Staphylococcus epidermidis* is reduced by 28-40 %. Bacterial proliferation on the surface of the catheter and biofilm production is also substantially reduced by the elution of free silver ions from the catheter matrix [62, 71].

Because the mechanical properties of catheters impregnated with silver in concentrations of more than 4-5% (w/v) deteriorate rapidly, the amount of silver which

can be incorporated into a polymer is limited. Topical application of high loadings of silver relating to polymer is range 1-2%. An increase in the release of free silver ions from the catheter can therefore only be achieved by an increase in the size of the active surface. This increase in surface can only be achieved - with identical concentrations of silver - by a substantial decrease in silver particle size. A smaller surface only has a reversible, bacteriostatic mode of action.

The antimicrobial activity of a surface is related to mechanisms that reduce bacterial adhesion and also to the active and continuous release of antimicrobial agents so that adherent microbes are killed. Polyurethane impregnated (0.7 % w/v) with submicron particles of metallic silver (particle size 20 nm x 20 nm) shows, in contrast to polyurethane alone and control catheters, hydrophilic properties. On the surface of the catheter impregnated with submicronic particles of silver a 28 % reduction in bacteria/ adherence compared to the basic material and a 40% reduction of adherence in comparison to conventional catheters was observed. Catheter samples incorporating metallic silver (2 % w/v) in a particle size of 1.2-2.5 μm were not hydrophilic and did not reduce adherence.

Solutions of chitosan almost completely inhibited all microbial species with less than 8 % viable cells remaining. The increased acidity of the control preparation solution also supported some antimicrobial activity with approx. 5 % inhibition and was demonstrated increased antimicrobial activity of chitosan solutions with increasing acidity [71].

In other study was investigated the antibacterial activity of PVC silver zeolite composites, tested on *Escherichia coli* and *Staphylococcus epidermidis* [17]. The results were promising both in culture broth and on agar plate and also in sterile urine seeded with these strains.

One great consideration should be given to raw materials and additives have been used in applications of plastic medical devices that will be FDA-compliant and free from heavy metals.

Silver is, for the most part, nontoxic. Silver is harmless to the body at bacterial effective levels. Humans take in about 70-88 μm of silver each day. Research suggests that 99 % of silver is readily excreted. Cases of extreme exposure have caused upper respiratory or mild eye irritation, and prolonged exposure can cause argyria. The antibacterial activity of silver-containing compounds used as antimicrobial coating for medical devices has been widely investigated but with conflicting results arising, especially *in vivo* [63]. However, silver oxide is an effective antimicrobial at levels as little as 1 ppm, so toxicity concerns are mostly irrelevant.

When designing an antimicrobial medical device, the topological and chemical characteristics of a medical device surface are important for the rate of microorganism adhesion. A perfectly smooth surface will be less likely to be populated than a rough surface, where more surface area is available as well as more adhesive force can be generated by the microorganism per surface area.

Also the chemical characteristic is essential for the initial population of a surface by free-swimming pathogens. Hydrophilic surfaces have been shown to be less quickly populated by free-swimming bacteria than hydrophobic surfaces [2].

The mechanical properties (tensile properties, density, hardness etc.) of the polymer are essential to ensure the optimal performance of the medical device**.** Each of applications requires materials with good defined physical, chemical, biological, biomechanical, and degradation properties to provide efficient therapies.

Within the scope of selecting the suitable material for a medical technical application, not only the technical requirements have to be considered, but often it is necessary to ensure the material is compatible with the human organism. Safety data can be obtained by testing according to validated methods described in ISO 10993 - *Biological Evaluation of Medical Devices*.

The requirements for this biocompatibility are complex, varying with specific medical applications. A material used satisfactorily in orthopedic surgery, for instance, may be inappropriate for cardiovascular applications because of its thrombogenic properties.

In some studies [48], biocompatibility of biomaterials is further classified according to their ability to induce a cause of cell or tissue death (cytotoxicity), to induce cancer formation (carcinogenicity), to damage genes (mutagenicity), to induce immune responses (pyrogenicity and allergenicity) or to induce blood clotting (thrombogenicity) [56].

Sterilization of medical devices has become increasingly because of the need to prevent patient exposure to infections caused by organisms on medical devices used during their care. The method of sterilization, however, must not interfere with the bioactivity of the material or alter its chemical composition which could, in turn, affect its biocompatibility or degradation properties.

The selection of an appropriate sterilization method is an important step in the use of polymer for biomedical purposes.

Sterilization can be done by a variety of procedures including steam sterilization, ethylene oxide sterilization, γ -irradiation, e-beam sterilization, UV exposure, and dry heat sterilization.

A lot of work has been reported on the effects of sterilization methods to the properties of several polymers [74]. In fact, each method has its own advantages and disadvantages. The method that may finally be used is dependent on many factors including the material to be sterilized and its resistance to the sterilization procedure.

Because of the high temperature range, autoclave or steam sterilization can melt the polymer or alter its morphological structure.

Energy methods such as gamma and e-beam irradiation are instantaneous, penetrating and non-toxic but may be associated with changes in the molecular structure. Although sterilization doses of radiation usually are on the order of 25 kGy, high-energy γ irradiation is used mainly in the healthcare industries to sterilize disposable medical equipment, such as syringes, needles, cannulas etc.

Plastic biomedical devices are usually sterilized by ethylene oxide (ETO). Ethylene oxide treatment is generally carried out between 30 ^{0}C and 60 ^{0}C, with relative humidity above 30% and a gas concentration between 200 and 800 mg/l, and typically lasts for at least 3 h. Ethylene oxide penetrates well, moving through paper, cloth, and some plastic films and is highly effective. ETO can kill all known viruses, bacteria, and fungus, including bacterial spores, and is compatible with most medical devices, even when repeatedly applied. ETO sterilization has its limitations as well it includes accelerated degradation of the polymer, and residual ethylene oxide gas within the bulk of the sterilized device.

6. Conclusions

In recent years there has been increased interest in using of antimicrobial medical devices for a specific or limited indication for use, such as reduction or prevention of a device-related infection, or reduction or inhibition of colonization of a medical device.

Each biopolymer and antimicrobial agent has different features, benefits, and limitations. It is important to choose the right antimicrobial and base polymer for each end use application to minimize any potential concerns. Manufacturers must choose antimicrobial agents that are compatible with their manufacturing process capabilities.

As conclusion, the development of antimicrobial medical devices can provides patients with safer hospital environment.

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