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Methods of incorporation antimicrobial agents in stents

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Abstract*— Commercial stents commonly used nowadays, especially metallic ones, present several disadvantages, such as corrosion, infection and restenosis, leading to health complications for the patient, or even to his death. Although there are different kinds of stents, like pharmacological stents, that can deliver drugs, there is not an "ideal" stent being able to avoid these disadvantages, of commercial ones. Thus, in order to minimize the reaction of human body and fight the adhesion of microorganisms to stent surface, some stent coatings have been developed. This review paper describes some antibacterial agents, like antibiotics, quaternary ammonium compounds (QACs), silver and silver nanoparticles, that can be coated on stent surface, in order to avoid infection, as also as their behavior in presence of bacterial microorganisms. Additionally, some results of incorporation of these antibacterial agents in implantable devices will be discussed. Finally, it will be designated some of principal methods of nanoparticles implementation, such as impregnation, layer by layer(LBL) technique, thiol chemistry and physical vapor deposition (PVD) method. The inclusion of antimicrobial agent in nanoparticles increases its antimicrobial effect, due to the major surface area.

Index Terms—**Antibacterial coatings, Nanoparticles implementation, Stents.**

I. INTRODUCTION

Cardiovascular diseases are a tremendous problem for public health, since they are a major cause of death worldwide in both sexes, and have high health care costs. Atherosclerosis of the coronary arteries is one of the most principal cardiovascular diseases and occurs when there is clustering of cholesterol (fat produced by the body) in the arterial walls, obstructing blood flow. Additionally, the accumulated cholesterol can cause a clot, leading to severe circulatory problems [1].

This type of heart disease can be treated by drugs, such as anticoagulants or antiplatelet agents, or by surgical procedures (angioplasties). In this procedure, a catheter, which has a small balloon at its end, is inserted in patient's blocked artery. The balloon catheter is positioned at the obstruction and inflated to lead to artery dilation [2]. However, although angioplasty is a very innovative technique, it has some disadvantages, including high rates of restenosis or reocclusion of arteries. Thus, stents have emerged as a mean of solution to this problem (Fig. 1).

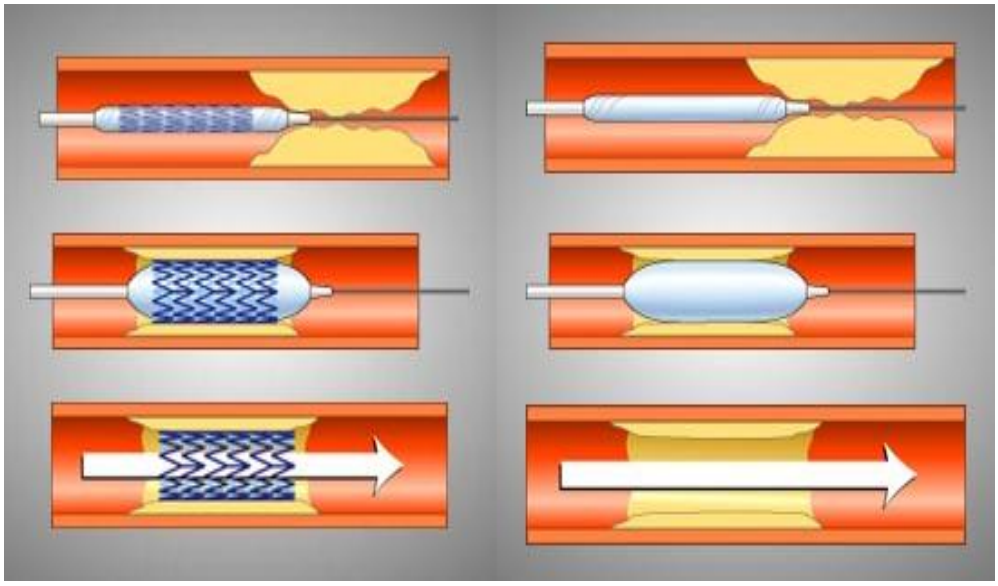

Fig 1- Angioplasty with stent (left) and conventional angioplasty (right) (image adapted from [2]).

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II. STENT COATINGS

A. Stents

Stents are rigid and perforated tubular structures, which are inserted into blood vessels in order to prevent or inhibit the constriction of blood flow, restoring the normal blood flow, when blood vessels are clogged, and are used in 70% of angioplasties [2], [3].

Cardiovascular stent was first used in 1986 in Toulouse, France, but its approval by the FDA (Food and Drug Administration) only occurred in 1994. Since then, stents have been evolved, in terms of implantation mechanism, materials, methods of manufacture and coatings.

These devices can be divided into conventional or pharmacologic stents. The first ones are endovascular fasteners, typically in metal, whose function is to maintain dilated artery. Pharmacologic stents belong to the second generation of stents and are available commercially since 2002. These stents are also metallic stents; however, they have the incorporation of drugs. Table 1 presents the advantages and disadvantages associated with different types of stents [2].

Table I-Advantages and disadvantages of conventional and pharmacological stents

Stents	Advantages	Disadvantages
Conventional	Low price, Reduced chance of late clots forming.	Higher rates of restenosis; Induction of trauma during deployment; Corrosion and the consequent release of ions to the body.
Pharmacological	Lower rates of restenosis.	Delay healing and increase endothelial inflammation; Higher rates of thrombosis; Price.

Stents must possess certain requirements, in order to, adequately, perform its function, such as biocompatibility (so that its use does not cause damage on the patient), mechanical strength, radiopacity (so that it is easy to view), longitudinal flexibility, ease of handling, corrosion resistance and having high strength and high radial expansion ability to recover [2], [4].

Stents can be made of different materials, but metals, particularly stainless steel, are the most common, due to its high tensile strength and corrosion resistance. However, metallic stents have low radiopacity. But, there are other metal alloys used in stents production, such as cobalt chromium alloy, which are radiopaque and biocompatible with high radial strength, and nickel-titanium, or nitinol [2].

Currently, there are, also, fibrous stents or stents with fibrous components: stents with fibrous structure combined with metal, stents coated with polytetrafluoroethylene (PTFE), polyester stents, polyamide stents, polyethylene stents, PTFE stents and poly (L-lactic acid) (PLLA) stents [2],[5].

The idea of using implantable fibrous structures is not new and the use of these materials in stents have been studied, because they eliminate the problem of corrosion and can minimize the occurrence of restenosis associated with metallic stents.

B. Infection and Biofilm Formation

Infection of medical devices can occur due to several reasons and from different sources of infection. Some of the most common sources of infection are: contaminated device surface, hands of medical staffs, and contact with others patients own skin or mucus membrane, among others.

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Many of these risk factors can be easily avoided, but infections are impossible to avoid completely. After the implantation of stents, or other implantable device, proteins, from the blood or tissue, get directly adsorbed onto the surface of stents. Moreover, the stent surface characteristics, such as, hydrophobicity, roughness, porosity and chemical composition, have direct influence on the protein adsorption [6].

The layer formed by adsorbed proteins has a very important role in bacteria's adhesion [7], [8]. The free swimming bacteria, in the so-called planktonic state, are adsorbed to these surface of proteins (Fig. 2 (A)).These bacteria then proliferate and recruit another bacterium from the surrounding environment (B), forming a colony in the surface, and change their gene expression pattern (C). This gene modification is responsible for the production of extracellular polymeric substances, which are essential in the formation of a biofilm (D) [9].

The biofilm slowly grows and small parts of it can detach and planktonic bacteria can escape from the biofilm and can invade new and clean surfaces at distant sites (E).

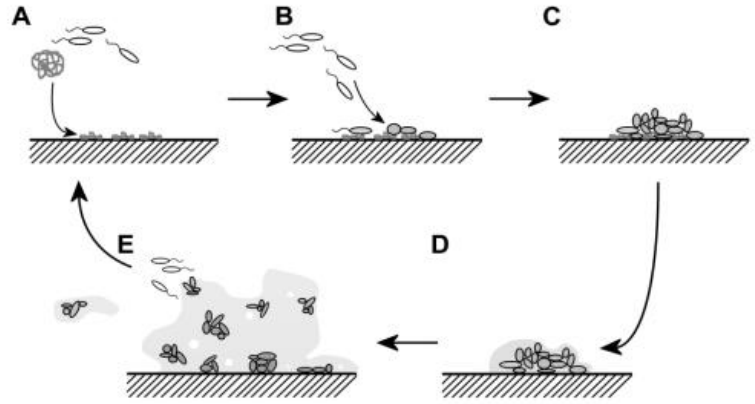

Fig 2-Biofilm formation (image adapted from [9]).

C. Stent Coatings

In order to minimize the limitations of available stents, many studies have tried to solve these problems through stent modification, by changing the stent material or modifying the stent surface, usually, with anticoagulants, antibiotics and antiplatelet. Through modification or coating of the stent surface, it is intended to improve stent's biocompatibility, by modifying their surfaces with less thrombogenic and inflammatory materials, and reduce the infection and the occurrence of thrombosis and restenosis, by coating the stent with therapeutic agents, which are released, gradually, over time, after stent implementation [10].Therefore, there are, mainly, three different types of stent coatings: biocompatible coatings, drug-delivery coatings and polymer-free coatings/surfaces [11].

Biocompatible coatings comprehend, mostly, inorganic materials, like silver, gold or carbon. These coatings have as main function, to increase the stent biocompatibility and to serve as a barrier to ion release by metallic stents. Usually, biocompatible coatings have no capacity to carry drugs**.** To avoid this disadvantage, biocompatible polymer coatings were developed, which can release therapeutic agents. These coatings can be no biodegradable polymers or biodegradable polymers like: poly(lactic acid) (PLA), poly(glycolic acid) and their copolymer, poly(lactic-co-glycolic acid) (PLGA). There are two drug-eluting stents approved by FDA: poly(ethylene-co-vinyl acetate) (PEVA) and poly(nbutyl methacrylate) (PBMA), and poly(styreneb-isobutylene-b-styrene) (SIBS). The first one is made of 316 L stainless steel and coated with a mixture of PEVA and PBMA, which contains sirolimus, to combat restenosis. In order to control drug release, a drug-free top coat of PBMA is applied. The second one is, equally, made of 316 L stainless steel, but it is coated with SIBS mixed with paclitaxel. Besides the good results showed by these stents, polymer coatings may lead to thrombosis and, in this way, polymer-free coatings/surfaces appeared. This approach uses nanoporous and microporous surface stents, as well as nanoparticles [11].Although nanoparticles have been extensively studied and applied as drug delivery system, the results of stent surface coated with them have few reports.

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Following, it will be described some therapeutic agents, with antimicrobial properties, which can be used in order to minimize infection and adverse reactions in the human body.

D. Antibiotics

The use of antibiotics has increased considerably after the discovery of penicillin. Antibiotics can be divided in two different types: bactericidal, when cell death is induced, or bacteriostatic, if just cell growth is inhibited. Antibiotics can inhibit DNA synthesis, bacterial protein synthesis or bacterial cell walls synthesis [12].

Although the use of antibiotics is associated with implanted medical devices, it shows some disadvantages. Antibiotics, normally, cannot reach the bacteria, since it is quite difficult for them to penetrate the formed biofilm in the implanted devices. Therefore, the concentration of antibiotics presented in the biofilm becomes very low, and this led to the development of bacteria´s resistance to antibiotics [13].

To increase the effectiveness of antibiotics, they can be applied locally on the implant surface, because bacteria are then killed directly before the biofilm formation. Some biodegradable coatings containing antibiotics can be used [10]. In that case, antibiotics are released at the time when these coatings get degraded. This approach is not viable for long term implants, once the concentration of antibiotics is finite. Therefore, after some time, the implantable device is again subjected to biofilm formation and consequent infection.

Despite antibiotics can be used in several medical devices, like sutures and catheters, the orthopaedic and trauma surgery areas are the ones where they are most used, being the most common gentamicin, vancomycin, rifampicin, and tobramycin.

There are some studies reporting the good results of antibiotic coatings in medical implants. A fracture fixation plate of PLLA was coated with rifampicin and was placed in tibia of rabbits. The implant showed good results, and 28 days after surgery presented acceptance of host-tissue and good antimicrobial properties.

Furthermore, minocycline and rifampicin were applied, directly, on titanium, to be placed on femur of a rabbit, and it showed noble results on prevention, colonization and infection after a week after surgery.

Reference [14] shows osteoconductive/osteoinductive/antimicrobial coating (HA (hydroxyapatite)/RGD (arginine-glycine-aspartate)/gentamicin) on orthopaedic stainless steel tibial implants, in rabbits, in order to evaluate *in vivo* effects of these coatings, bone formation, biocompatibility and implant integration. The study comprehended 45 rabbits, 6 animals for the group of Gentamicin- HA implants, 6 for the group of Gentamicin –RGD implant and 6 for control group, of pure HA, for 4 weeks and 9 rabbits of each of the mentioned groups for 12 weeks. Table II shows the principal results of the study, where is not evidenced significant differences between the three groups studies.

Table II- New bone formation on the implant surface (table adapted from: [14])

	New bone formation on implants surface (%of implant length)	
	4 weeks	12 weeks
HA	7,89 ±6,8	33,8±12,8
HA-Gentamicin	11,0±7,38	24,7±19,0
RGD -Gentamicin	3,87±4,5	25,1±19,3

The tests showed, also, that 95 and 99% of gentamicin were released, respectively, after 12 and 24h, as shown in Fig. 3. Overall there were no statistical significant differences between the three studied groups; however there was a general trend towards impairment in bone formation in implants coated with gentamicin. More recently, a study on antibiotic releasing tibial nail reported promising results in infection, after six months of implantation. The great disadvantage of antibiotic coatings is the increasing number of antibiotic-resistant bacterial [15]. In general, the use of antibiotics as antibacterial agents, in implantable devices, is controversial and may not be the best solution [9].

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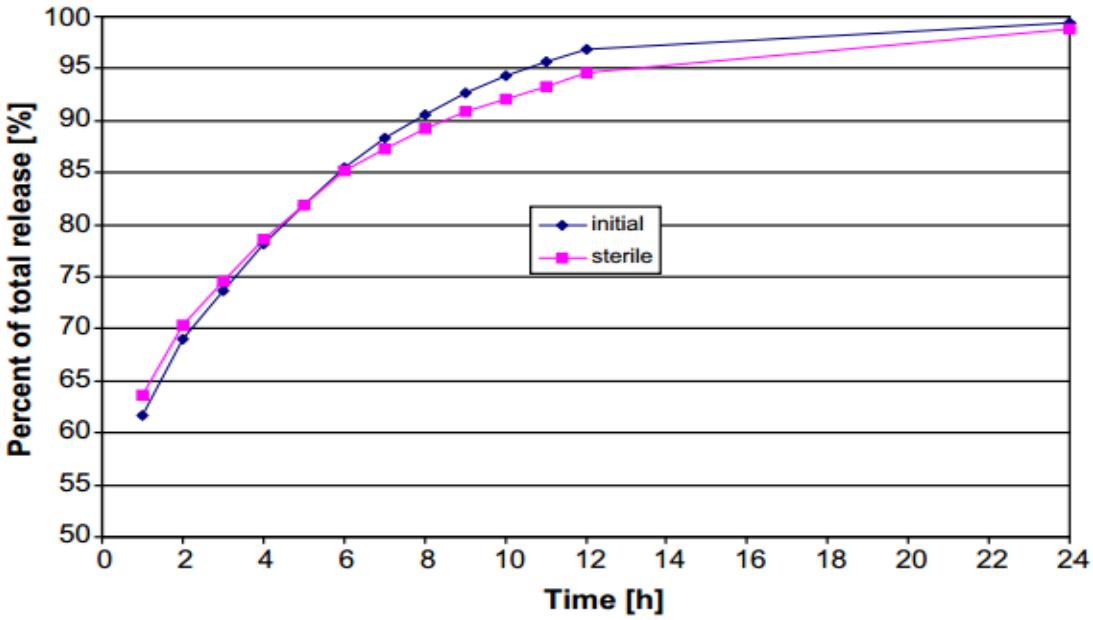

Fig 3- Elution kinetics of gentamicin from the implant surface at a [250] mgm^{-2} (figure adapted from[14]).

E. Quaternary Ammonium Compounds (QACs)

QACs are used as antimicrobial agents and are very popular since it is very easy to manufacture these compounds in large scale as well as to modify their surface area. These compounds are used as antimicrobial compounds since 1935 and can be used as disinfectants also (Fig. 4).

The antibacterial effect showed by QACs can be explained by two different mechanisms. In the first one, the presence of positive charge on a surface can release cations to the bacteria wall, and in this way, break the external membrane of bacterium. In the second suggested mechanism, the cationic surface can change its configuration and, in this way, lead to the bacteria's lysis.

In respect to the mechanism, the presence of a positive charge on QACs has a negative effect on cell survival in general [16], [17]. On the other hand, QACs, when come in contact with bacteria, will reduce their viability and cells will die. Moreover, QACs can cause antimicrobial resistance, which decrease their efficiency. Thus, the application of QACs is still very limited as antimicrobial surface coatings for medical implants [9].

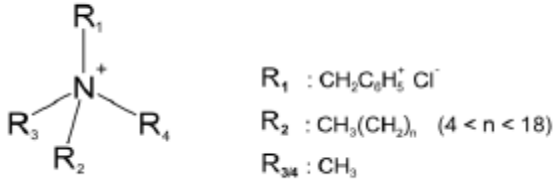

Fig 4- Quaternary ammonium compounds only have antimicrobial activity if the alkyl chain (R2) contains between 4 and 18 carbon atoms (figure adapted from [9]).

Reference [18] reports the efficiency of central venous catheters coated with Benzalkonium chloride (BAC) against *Candida albicans* and colonization of gram positive and negative species. This compound also showed good results in orthodontic materials against *Streptococcus* micro organisms. Another application of QCA was demonstrated by [19], where prostheses of polytetrafluoroethylene (PTFE) were coated with hydrophilic antibiotics drugs bonded with QAC compounds and, after the prosthetic implantation, antibiotics were delivered.

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F. Silver

The use of novel metals, for example silver, is one of the most used strategies to prevent the adhesion of microorganisms to stent, or other implantable device surface.

Silver has been used for centuries as an antimicrobial agent. From the medical point of view, silver was used by ancient Egyptians, Greeks and Romans to clean wounds. The use of silver in medical applications has grown until 1940, when penicillin was introduced for infection treatment. However, in 1968, silver nitrate was combined with sulphonamide to form silver sulfadazine (AgSD). This compound became the best known use of silver as an antibacterial agent and for treatment of burns. AgSD is like a reservoir of silver that slowly releases silver ions, causing membrane bacterial damage [20].

The antimicrobial effect provided by silver depends on the amount of silver and the rate of released silver. Silver can be present in diverse forms: as metal, as a compound or as a free dissolved ion. Nevertheless, to present anti-microbial activity, the ionization of silver in Ag^+ form is required. In metallic state, silver is inert but it reacts with moisture and fluids from the wounds and gets ionized.

The exact mechanism of antimicrobial action of silver is not known yet, but there are some possibilities. In metallic state, silver interacts with thiol groups present in the bacterial cells and inhibits the respiratory process, leading to the cell death.

In some specific bacterium, such as *Escherichia coli*, the antimicrobial effect is provided by the inhibition of the uptake of phosphate and release of phosphate, mannitol, succinate, proline and glutamine [20]. In case of silver ions, the antimicrobial properties are due to structural and morphological changes. Silver ions can penetrate inside the bacterial cells impeding the DNA replication and, consequently, leading to the cell lysis.

Moreover, silver ions have a far lower propensity than classic antibiotics to induce antimicrobial resistance [21]. Besides the anti-microbial properties exhibited by silver, it can be toxic to organisms after a prolonged contact to silver ions [22].Despite all medical applications of silver and silver ions, the information about it toxicity is limited. However, some studies demonstrated that some forms of silver, especially silver ions (Ag^+), are more toxic than other forms [9]. The toxicity of silver can be observed in the form of argyria, which is an irreversible disease that discolours the skin. The ophthalmologic system can also suffer from prolonged exposure to silver resulting in a condition called argyosis [9], [20], [23].

As the toxicity of silver is dependent on the availability of free silver ions, investigations have shown that the commonly used concentrations of Ag^+ are too low to lead to toxicity. Metallic silver appears to pose minimal risk to health, whereas soluble silver compounds are more readily absorbed and have more potential to produce undesirable effects [23].

G. Silver Nanoparticles as an antimicrobial agent

Among all strategies for providing antimicrobial properties to implantable devices, like stents, the use of silver is one of the most common and effective techniques.

Silver directly incorporated into implantable devices' surface can be released very quickly, limiting the time period of antibacterial protection. Thus, the need arises for the incorporation of silver nanoparticle which may coat the implantable device surface and increase the time period of silver's antimicrobial activity [24].

Silver nanoparticles can reduce colonization, infection rate, hospitalization days, and present economic benefits and are more efficient in antimicrobial aspects than silver salts due to their enormously large surface area, which provide better contact with the micro organisms [9].

As mentioned previously, the mechanism of antibacterial action of silver is not absolutely clear. The silver nanoparticle's efficacy depends on the size and shape of particles. Small silver particles (<10nm) and triangular shaped particles demonstrate higher antibacterial activity as compared to big and spherical particles. Small silver nanoparticles produce electronic effects through the interaction with bacteria, and this intensifies the reactivity of

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nanoparticles [23]. According to [25], triangular shaped nanoparticles are a better option since they need less amount of silver to show bacterial inhibition. While triangular nanoparticles need 1µg of silver, the spherical nanoparticles need 12.5 µg and rod shaped nanoparticles need 50 to 100 µg [20].Stents and other implantable medical devices with silver nanoparticles incorporated on their surface slowly release silver ions in to the coating layer and, subsequently, in to the solution. When in contact with bacteria and chemical compounds of their metabolism, the Ag dissolution increases and, consequently, bacterial inhibition is more effective (Fig. 5).

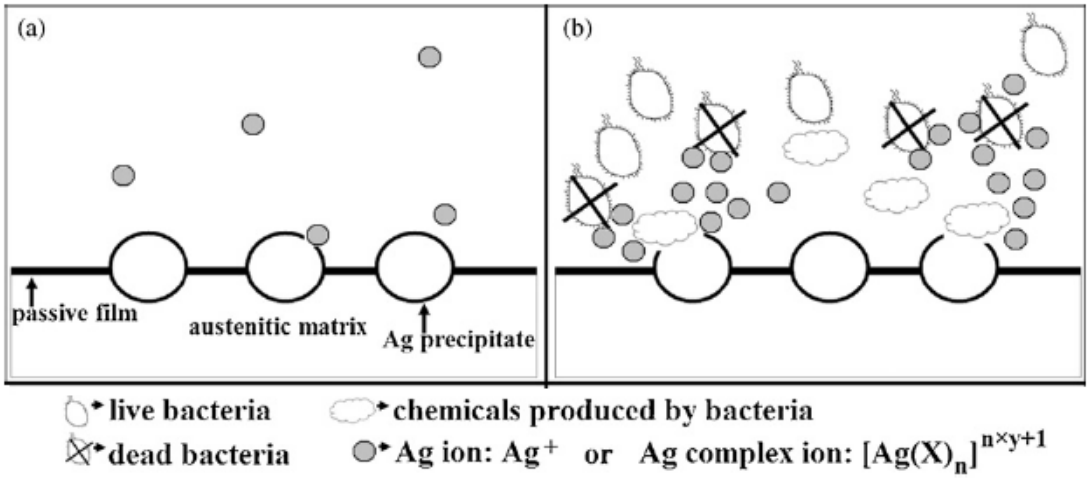

Fig 5- Silver antibacterial mechanism (image adapted from [26]).

The concentration of silver ions required for optimal antibacterial effect is observed between 10nM and 10µM [9]. In reference [27] NP were deposited on metallic stents surface and drug release kinetics was evaluated and they conclude that NP-eluting stent is a potential innovative method.

Several synthesis techniques were developed to obtain silver nanoparticles with different shapes and sizes, such as laser ablation, gamma irradiation, and electron irradiation, chemical reduction by inorganic and organic reducing agents, photochemical methods, microwave processing and thermal decomposition of silver oxalate in water and in ethylene glycol. The efficiency of antimicrobial properties is dependent on synthesis technique also. In last few years the applications of silver nanoparticles in medicine field have been rising [23].

III. METHODS OF NANOPARTICLES IMPLEMENTATION

Nanoparticles present a wide range of applications, which make several developments in terms of shape and substrates where they are incorporated (metals, carbon, metal oxides, fibrous materials, etc.).

Due to the novel properties of nanoparticles, their incorporation into fibrous materials has been intensively investigated. Generally, silver nanoparticles are deposited, impregnated or coated onto medical devices for controlling infections. With the advance of nanotechnology, new techniques are used to coat the medical devices with thin layers of silver nanoparticles, such as physical vapour deposition (PVD) [28].

A. Impregnation

Impregnation is one of the most old and simple methods of incorporating antimicrobial agents into textile fabrics. For example, it has been used for application of silver nanoparticles on to cotton fabrics.

This technique is extremely simple and can be used in clinical situations, since it only requires $AgNO_3$, butyl amine and absolute ethanol. The antimicrobial activity is controlled by the concentration of reactants used.

Impregnation can be applied in fibrous materials. For example, dried cotton fabrics have cellulosic walls containing OH groups on the surface of cotton. Therefore, cotton can be functionalized through its immersion in the solution described above. The bonding with OH groups will reduce silver and provide an antimicrobial activity (Fig. 6) [29].

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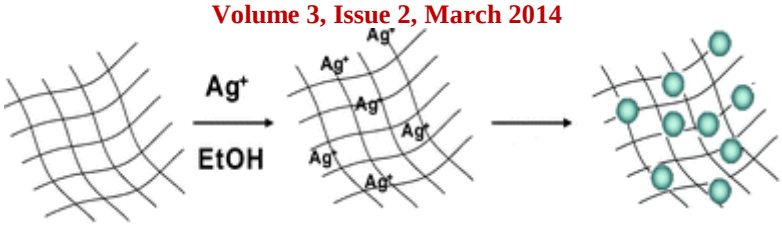

Fig 6 - Example of silver impregantion (figure adapted from [29]).

However, using the impregnation technique, the rate of the deposition of nanoparticles on the substrates is low and nanoparticles can be released due to weakness of interactions between nanoparticles and fibres [28].

Nevertheless, [30] created nanoparticles based on biodegradable polymer (with 290 nm of diameter), and impregnated with magnetite, which responds strongly to a magnetic field. The major advantage of using biodegradable polymer is the ability of the nanoparticles to break down and release drugs, inside the body. The researcher implanted a stainless steel stent into arteries of live rats and then injected the biodegradable nanoparticles loaded with paclitaxel and produced a uniform magnetic field. The magnetic field magnetized the stent and the nanoparticles and conducted the nanoparticles into stent surface. After the study, the author concludes that the restenosis rate was considerably lower.

B. Layer by Layer

Layer by layer (LBL) technique was introduced in 1991 and since then it became one of the most popular techniques for preparation of nanoscale films with tailored properties.

The principle of layer by layer technique is based on the alternating adsorption of materials containing complementary charged or functional groups to form integrated thin films.

Normally, this technique begins with the adsorption of a species having opposite charge of the substrate and this reverses the charge of the substrate. This process is repeated forming several layers, until the desired thickness is achieved (Fig. 7) [31].

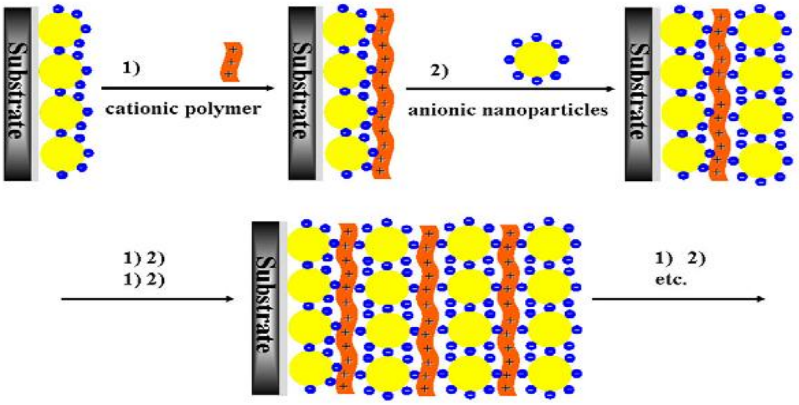

Fig 7- Layer-by-layer technique (figure adapted from [32]).

The film properties can be controlled by varying the type of species adsorbed, the number, and, consequently, the thickness of layers and the conditions employed during the assembly process.

The great advantage of this technique is that it allows a variety of materials, such as polymers, nanoparticles, proteins, among others; to be assembled on different substrates and the attachment can be through electrostatic interactions but also through hydrogen bonding, hydrophobic interactions, covalent bonding, and complementary base pairing [32].

This technique has been studied and employed on stents, by deposition of a thin film. For example, LBL assembly on nitinol surfaces facilitates the incorporation of nitric oxide donor and, this way, the bacterial adhesion is reduced [33].

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Reference [34] used self-assembled monolayers (SAMs) to incorporate and deliver therapeutic drugs (prednisolone as model drug) from stent surface into human body. SAMs are ordered nanosized molecular coatings, which add 1 to 10 nm thickness to a surface (Fig. 8). The study showed that monolayers with a few monometers thick can preserve the chemical groups on the surface and can persist on surface of stainless steel stents for 14 to 21 days, before oxidation and desorption of the thin film [34].

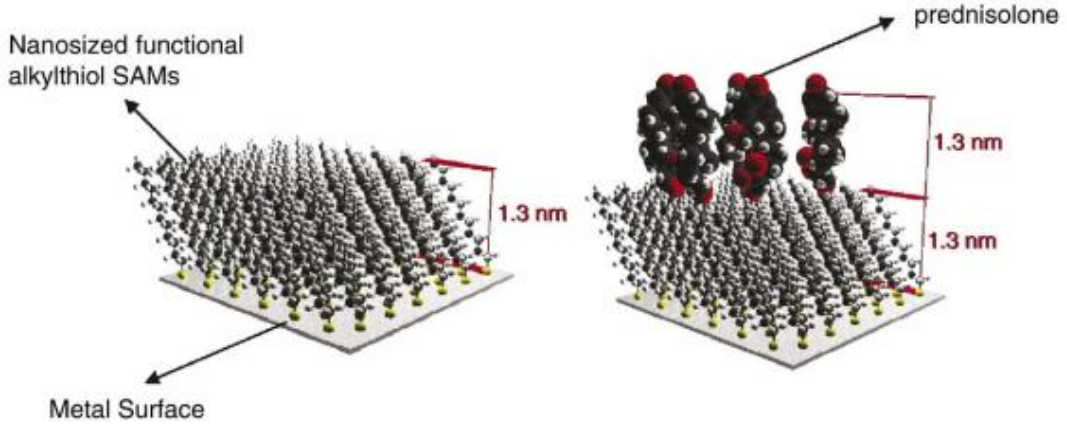

Fig 8- Representation of nanosized functional SAMs used as tethers for drug attachment and delivery for cardiovascular stents (image adapted from [34]).

C. Covalent (thiol chemistry)

In the last few years, the deposition of metallic nanoparticles, on to polymeric substrates is being practiced increasingly due to their strong antimicrobial activity [28].

In order to modify surface properties or to fabricate self- assembled monolayers, the adsorption of thiol molecules, especially on noble metals, like silver and gold, are being studied.

The adsorption of thiol occurs in several steps, starting with physical adsorption, then sulfur-metal bonding reaction, followed by the orientation of adsorbed molecules and, finally, the formation of a compact self –assembled layer (Fig. 9) [35].

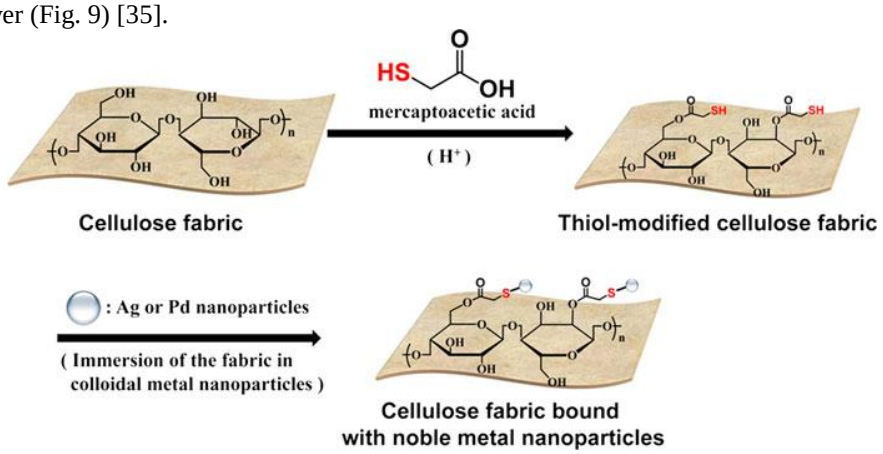

Fig 9- Example of covalent attachment (figure adapted from: [28]).

Some properties of metallic nanoparticles, such as biomedical and optical functions, are influenced by thiol adsorption.

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D. Physical Vapor Deposition

One of the most widely used techniques for the functionalization of biomaterials is Physical Vapor Deposition (PVD). This technique is used in stents, due to its ability to place a thin film onto non-uniform geometry. PVD provides strongly adherent films and optimal adhesion and integrity upon stent expansion [36].

PVD comprises a number of deposition techniques all of which allow transport of materials in the solid state between the target and the substrate (the material to be coated). This entire process must occur under vacuum, to prevent material contamination.

One of the principal techniques of PVD is sputtering whose purpose is the controlled transport of atoms between a target and a substrate on which will take place, at an atomic level, the formation and growth of a thin film, which will be the coat [37].

In this technique, the target is bombarded with ions gas (with plasma formation) which will lead to the ejection of atoms of target material to be transported and deposited on the substrate [38]. Sputtering presents some advantages such as:

- Sputtering target provides a stable and extended lifetime source;
- It is possible to use reactive gases, such as nitrogen, oxygen, acetylene and silane;
- Ecological process.

In this technique there is magnetron, radio frequency or pulsed source sputtering. The magnetron sputtering is used in 90% of PVD techniques [36].

Magnetron Sputtering

Magnetron sputtering uses a magnetic field, formed by the introduction of magnets, which are placed in parallel to the target and perpendicularly to the electric field, causing an increased flow of electrons around the target.

The magnetic field induces a circular movement in electrons, and, in this way, increases the probability of collision between electrons and ions of the gas. With the increased ion density, due to the increased number of collisions between the electrons and gas atoms, the deposition rate increases [38].

The major disadvantage of this process lies in the fact that the target material is only used in 20-30%. In contrast, the magnetron sputtering allows controlling effectively the deposition parameters and the quality of coatings and reduces the impurities in the film [37], [38].

Reference [39] compared a titanium-nitride-oxide coated stent with a commercial stainless steel stent. A stainless steel stent was coated by PVD technique, with titanium in a gas mixture of nitrogen and oxygen. The resulted stent was immersed in albumin to sterilize and prevent oxidation. In the end of the study, the authors concluded that titanium-nitride-oxide coated stent showed better results, namely, it reduced restenosis and other adverse cardiac events, when compared with stainless steel stent.

More recently, [40] coated a cobalt chromium alloy coronary stent with diamond like carbon (DLC), by physical vapour deposition, in an attempted to promote quickly endothelisation of stent and low platelets activation, in order to minimize thrombotic clots. The stent was implanted in a pig artery and the results were compared with a cobalt chromium alloy coronary stent without coating. From SEM images (Fig.10) it is possible to notice a perfect endothelisation (98%) in coated stent, while in uncoated stent the rate of endothilisation was only 65%.

The results confirmed that DLC coating present a favourable haemo compatibility and non-inflammatory behaviour and DLC-coated Co–Cr stents showed a homogenous endothelisation and inhibited the platelets activation, which resulted in a stabilisation of the vessel healing in 30 days and minimal proliferation after 180 days.

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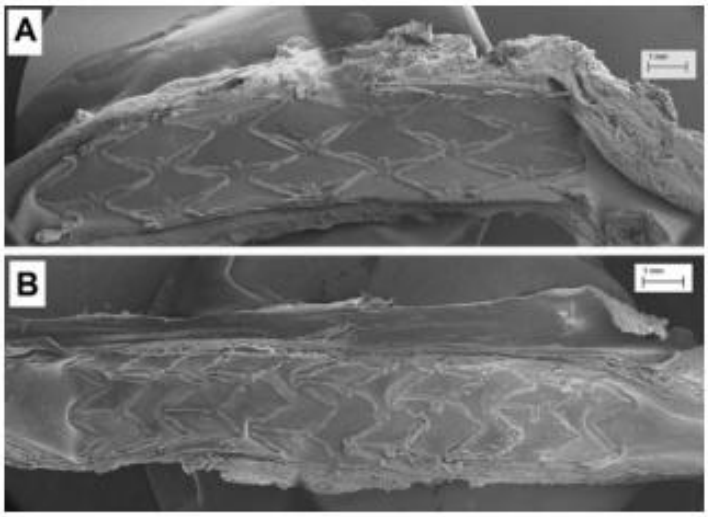

Fig 10- SEM images (x35) after 7 days of stent coated (A) and uncoated stent (B) implentation (image adapted from: [40]).

IV. CONCLUSION

The surface modification and inclusion of antimicrobial agents in stents is a major innovative advancement, since, in this way, problems like restenosis, infection or review surgeries can be avoided. Antimicrobial coatings reduce the adhesion and proliferation of microorganisms into stent surfaces, promoting the health and well-being of the patient. Mmainly, three different types of stent coatings such as biocompatible coatings, drug-delivery coatings and polymer-free coatings have been explored. Biocompatible coatings mostly use inorganic materials like silver, gold or carbon and increase the stent biocompatibility as well as act as the barrier to ions released by metallic stents. However, these coatings usually do not have the ability to carry drugs and therefore, drug-eluting stents based on biodegradable (such as PLA, PGA, PLGA, etc.) or non-biodegradable polymer coatings have also been developed with promising results. To avoid the risk of thrombosis that may occur due to these polymer coatings, polymer-free coatings are also tried.

Although the use of surface coatings containing antibiotics have been found to provide good results in some studies, its use is not generally considered to be the best approach as it may increase the number of antibiotic-resistant bacteria. Due to similar reason, the use of Quaternary Ammonium Compounds is also very limited as antimicrobial surface coatings for medical implants, although they can be manufactured and applied very easily. In contrast to the above two cases, silver has lower propensity to induce antimicrobial resistance and is one of the most used strategies to prevent the adhesion of microorganisms to stent, or other implantable device surface. However, toxicity related to use of silver is a serious concern, although investigations have shown that the commonly used concentrations of Ag+ are too low to lead to toxicity.

Among all antimicrobial agents, the use of nanoparticles is one of the most effective techniques, due to their huge surface area, which implies better contact with microorganism and, therefore, provide better protection against them. Nanoparticles such as silver can reduce colonization, infection rate, hospitalization days, and present economic benefits and are more efficient in antimicrobial aspects than silver salts. The methods of nanoparticle incorporation has been intensively investigated and several techniques such as impregnation, layer by layer, covalent, physical vapour deposition, magnetron sputtering, etc. are used to coat implantable device with thin layers of nanoparticles.

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