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A Systemic Review on Preparation of Anti-Bacterial Bio-Materials by Using Plasma Surface Modification Techniques

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ABSTRACT:

Plasma based procedures offers many benefits for creating anti-bacterial bio-materials. It can be administered directly or combined with other surface modification techniques. Direct plasma strategy is a part of plasma surface modification which produces anti-bacterial activity by tailoring surface topography or surface chemistry. Anti-bacterial effect by tailoring surface chemistry via plasma can be attained by either creating bacteriostatic surfaces or bactericidal surfaces. By using plasma immersion ion implantation (PIII) to alter medical grade poly vinyl chloride covered by triclosan or bronopol to improve anti-bacterial properties. The plasma modified polyvinyl chloride with bronopol displays great anti-bacterial property. The plasma modified poly vinyl chloride with triclosan has preferred anti-bacterial performance against Escherichia coli (gram negative) or Staphylococcus aureus (gram positive) over bronopol.

KEYWORDS:

Plasma techniques,surface modification, plasma immersion ion implantation, Anti-bacterial coating, Medical poly vinyl chloride, Triclosan, Bronopol.

I. INTRODUCTION:

1.1 Plasma surface treatment:

- Plasma surface treatment is a process that raises the surface energy of many materials so as to the bonding characteristics.
- Plasma treatment is a process by which a gas is ionized in a vacuum chamber to form plasma and alter the surface of the material.
- This process is performed in the plasma chamber under vacuum pressure.
- Oxygen plasma treatment is an example of vacuum plasma surface treatment.

1.2 Plasma surface modification:

- Surface modification is the act of modifying the surface of a material by bringing physical, chemical or biological characteristics different from the ones originally found the ones originally found on the surface of a material.
- The main purpose of surface modification to inhibit oxidation and promote adhesion of further coatings, or reduce staining.

1.3 Biomaterials:

- A biomaterial is a substance that has been engineered to interact with biological systems for medical purpose, either a therapeutic or diagnostic one.
- As a science, biomaterials are fifty years old.
- The study of biomaterials is called biomaterial science or biomaterial engineering.
- Biomaterials are used in breast implants, bone plates, dental implants for tooth fixation, surgical mesh, etc.

1.4 Polymers:

- A polymer is a substance or material consisting of very large molecules called macromolecules, composed of many repeating subunits.
- Due to their broad spectrum of properties, both synthetic and natural polymers play essential role in everyday life.
- According to IUPAC, a polymer is a substance composed of macromolecules. A macromolecule is a molecule of high relatively molecular mass.
- Proteins, cellulose and nucleic acids are some of the examples of polymers.[1]

II. PLASMA SURFACE STRATEGIES:

Plasma strategy offers more benefits for producing antibacterial biomaterials and can be used directly or combined with other surface modification techniques. The risk of infection being achieved during every implantation techniques. Implantation related infections (IRI) cause severe morbidity and mortality to the

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patients. The risk of IRI depends on many factors such as the material, surgical technique, tissue where the biomaterial is used [2]. Many surface modification techniques are being used to create antibacterial surfaces to decrease the rate and extent of IRI. They are classified as active and passive strategies. The active strategybrings antibacterial effect by releasing bactericidal agents such as antibiotics. In case of passive strategy the bacteria can be prevented from adhering to the surface and/or killing bacteria upon surface contact. Bacterial colonization can be prevented in passive strategy by tailoring surface physiochemical properties such as surface chemistry, topography, energy, etc [3]. Antibacterial surfaces can be classified as bactericidal or anti-biofouling. Bactericidal surfaces has an advantage of bactericidal agents causing cell death that can either be released or not released from the surface, and anti-biofouling surfaces resist or repel the initial attachment of bacteria according to their physicochemical properties such as electrostatic repulsion, surface energy, etc[4]. Surface modification techniques should be tailored according to the properties of the material of interest, such as solubility, temperature sensitivity, corrosion properties, mechanical properties, etc. Environmental effect, scalability, cost and integration to industrial production line should also be taken in account [5]. The advantages of this method are that can provide uniform and reproducible surfaces, and a large variety of gases and monomers can be used in plasma. The plasma techniques have become a very suitable method for large scale industrial production. Gaseous plasmas are ignited by applying a through a gas and can be generated in either low pressure (LP) or atmospheric pressure (AP) [6]. LP plays an important role in biomaterials research since at LP, the discharge is more stable and the plasma reactions can be controlled very easily. The interaction between LP and AP results in three processes namely plasma treatment, plasma polymerization, or plasma etching can occur. In plasma treatment, inert gases such Argon, Helium, Nitrogen are widely used to create functional groups or radicals on the surfaces, which are used to improve adhesion of the surfaces [7]. Antibacterial agent such as antibiotics gets grafted during plasma treatment with the help of surface functional groups or surface free radicals [8]. A plasma deposited coatings can exhibits direct antibacterial activity by an anti-fouling mechanism. Here the bacterial adhesion and biofilm formation prevented by creating specific surface chemistries that inhibit bacterial attachment [9].

TYPES OF PLASMA STRATEGIES:

- **Direct plasma strategies:**

a) Tailoring the surface topography
b) Tailoring the surface chemistry

- **Plasma assisted strategies:**

a) Plasma coating as drug eluting reservoirs and diffusion barriers.
b) Plasma surface for grafting antibacterial agents.
c) Plasma surface activation for improving the adhesion of antibacterial coatings.

2.1 DIRECT PLASMA STRATEGIES:

2.1.1.Tailoring the surface topography:

Surface topographical features can affect the behaviour of eukaryotic and prokaryotic cells on the surfaces at the micro and nanoscale [10].Plasma nanoscience is an emerging and promising area, and one of its applications is biomaterials [11].A strategy combining plasma-induced changes in surface chemistry and surface topography can tackle biomaterial-related infection and biocompatibility challenges [12].The different adhesion characteristics of the osteoblastic and bacterial cell arise from these cells' different inherent properties. Eukaryotic osteoblast cells have nano-scaled structures that can detect and anchor on the surface's nano topographic features. In contrast, prokaryotic bacteria cells have a more rigid cell wall that makes them less able to conform and attach to surface nanostructures. As a result, the growth of bacterial cells is inhibited while the growth of mammalian cells is promoted [13].Similarly, Hasan et al. reported that anisotropic nanostructures created on the Ti surface exhibit high antibacterial activity against P. aeruginosa and E. coli (98% ± 2% and 95% ± 2%, respectively) (Fig. 1).

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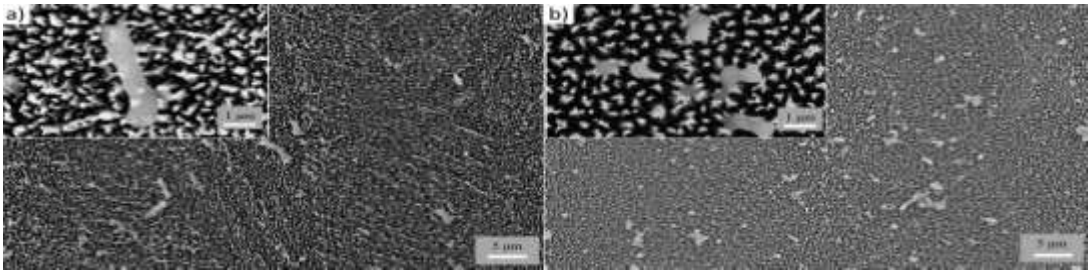

Fig.1. The anisotropic nanostructures created on the Ti surface exhibits antibacterial activity by disturbing the cell wall of a) P. aeruginosa and b) E. coli. adapted from Hasan et al Licensed under a CC BY 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

The nanostructures resembled nanopillars with a height of approximately 1 μm, a diameter of about 80 nm and a random spacing between individual nanopillarosteogenic differentiation was induced (Fig. 2).

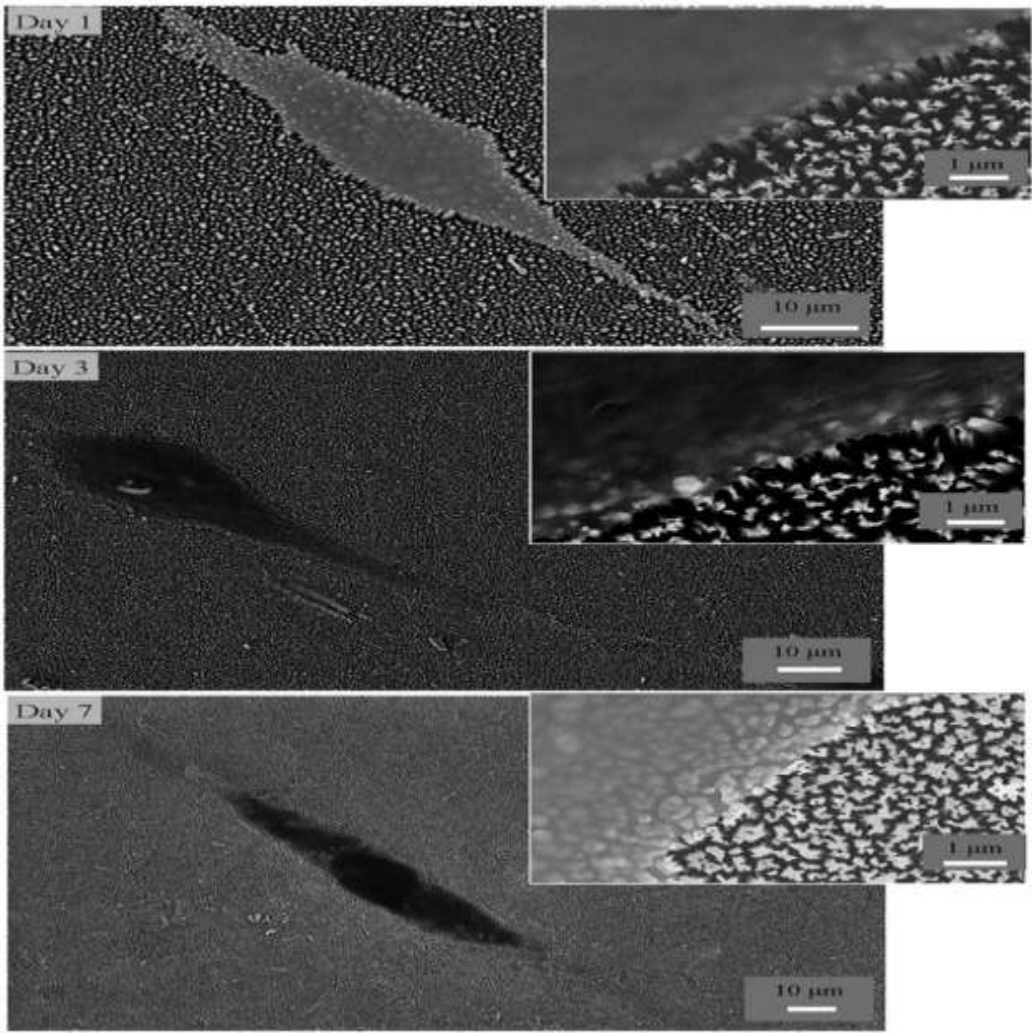

Fig. 2. The anisotropic nanostructures created on the Ti surface enhanced the attachment, proliferation, and osteogenic differentiation of human mesenchymal stem cells.

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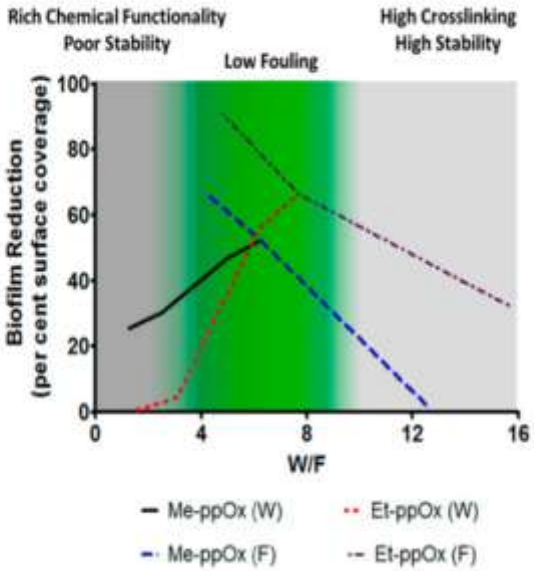
Surface roughness, topography, charge, and wettability all play a complex role in bacterial adhesion, and the surface nano topography isn't always the predominant factor affecting the antibacterial property [14]. Direct plasma treatment yielded a superhydrophilic continuous oxide film containing nanograins. For the indirect treatment, a surface morphology resembling a chemically etched surface was achieved with pyramidal growths arising from the nucleation of TiO or TiN with a moderately hydrophilic surface property. Both treatments caused an increase in surface roughness [15].The cell membrane of adhering bacteria deforms by conforming to the topography in and around the spikes. The deformation of the cell wall is responsible for the antibacterial effect causing a reduction in the viable bacterial cells in the incubation medium as well [16]. On the contrary, the bacterial adhesion on hydrophobic nano-rough surfaces is lower, and as a result, the amount of viable bacteria in the incubation medium is higher. The factors appearing to reduce the viability of S. aureus were found to be a nanostructure having positively charged surface chemistry and WCA of 70◦ or less. The surface structure can have a more prominent effect than the surface roughness and should be taken into account when morphology-based approaches are considered for imparting antibacterial activity [17].

2.1.2 Tailoring the surface chemistry:

2.2.1.1 Plasma generated anti – fouling surfaces:

Bacterial adhesion and biofilm formation can be prevented by creating specific surface chemistries that inhibit bacterial attachment (non-fouling). Poly(ethylene oxide) based coatings have been extensively used for the generation of antibacterial surfaces and are considered as the "gold standard" due to their excellent antifouling properties [18].Cavallaro et al. produced plasma polymerised antibacterial POx coatings using 2-methyl-2-oxazoline (Me-Ox) and 2- ethyl-2-oxazoline (Et-Ox) as precursors. When the deposition power has been varied, substrates having lesser chemical functionality retention of the precursor showed higher antifouling properties. Due to the complex nature of bacteria-surface interactions, the antibacterial activity of plasma polymerised films with different chemical functionality retention of the precursor could not be explainestraight forwardly (**Fig. 3**) [19].



2.1.2.2 Direct deposition of anti – bacterial agents:

Bacterial adhesion and biofilm formation can also be prevented by killing bacteria upon contact with the surface (contact-killing). Such surfaces can be produced by incorporating antibacterial agents, including synthetic antibiotics, natural antibacterial substances, or inorganic antibacterial agents. Plasma techniques provide the advantage of direct deposition of antibacterial

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agents to materials surfaces eliminating the need for multistep procedures that use high amounts of chemicals such as solvents and crosslinkers. Disadvantages of incorporating synthetic antibiotics agents onto biomaterial surfaces have been reported as the possibility of antibacterial resistance, a limited amount of antibiotic that could be included onto the surface, and limited specificity of antibiotics [20]. Inorganic antibacterial agents, such as Ag and Cu, have been proposed as alternatives to synthetic antibiotics since they have a broad spectrum of antibacterial activity at low concentrations.It is also possible to include Ag to surfaces using direct plasma strategies. Wang et al. used an aerosol-assisted APP deposition system to produce a nano-capsule consisting of an AgNO3 core and a hexamethyldisiloxane (HMDSO) shell-based antibacterial coating that releases Ag+ ions (Fig. 4) [21].

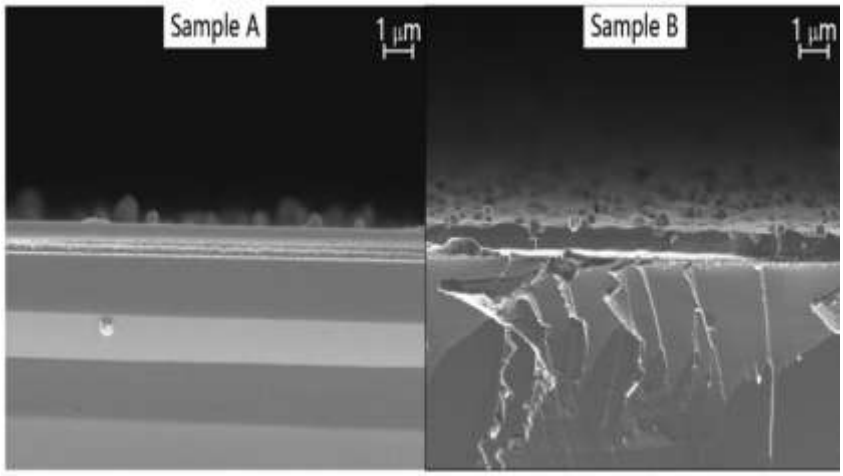

Fig.4. SEM cross-sectional images of Ag containing HMDSO shell-based coating using HMDSO: AgNO3 aerosol flow rate of 1:1 for sample A and 1:5 for sample B. Reprinted from Wang et al with permission from Elsevier. Copyright © 2020 Elsevier [21].

2.1.3 The effect of surface chemistry Vs surface topography:

Surface chemistry, e.g. SFE, hydrophilicity, surface charge, and surface morphology, e.g. roughness and hierarchical arrangement of nano- and micro-features, can affect the bacterial adhesion and biofilm formation on materials surface. Antibacterial activity may result from solely the effect of surface chemistry or surface morphology or can arise from the synergistic effect of both [22]. Most bacteria's cell wall is negatively charged, and it's generally accepted that surfaces with a negative charge will prevent the adhesion of negatively charged bacterial cells by electrostatic repulsions. By increasing the density of negative charge on the surface, the intensity of repulsive forces can increase [23]. Surface treatments such as oxygen plasma can introduce negatively charged functional groups such as □ COOH and □ OH on the surfaces that can resist the adhesion of bacterial cells having negatively charged cell wall. These functional groups can also increase surface hydrophilicity [24]. The relationship between the adhesion of mouse embryonic fibroblast cells Vs WCA with an exponential model and the relationship between cell adhesion and surface roughness with a linear model (Fig. 5).The surface roughness of a starting material can contribute to different functional groups' distribution along the surface and result in diverse final surface topography after plasma coating even when using the same precursor and same plasma conditions [25]. A stronger field is obtained around smaller-scale structures and a weaker field around larger structures. This imbalance in the electric field is concluded to cause the heterogeneity of the chemistry and thickness of the plasma deposit. When the surface features have a bigger size, the electric field becomes even weaker and cannot promote the formation of a coating because it is not strong enough to drive ion flux from the plasma sheath to the surface [26].

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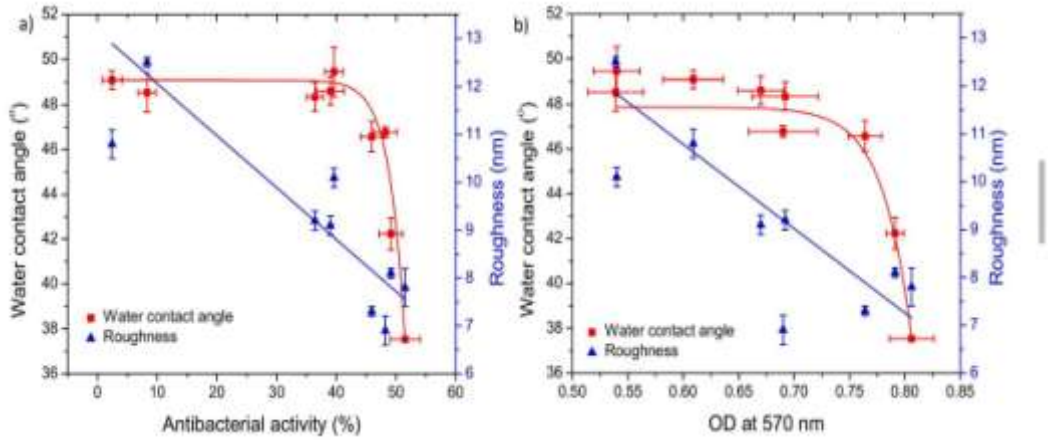
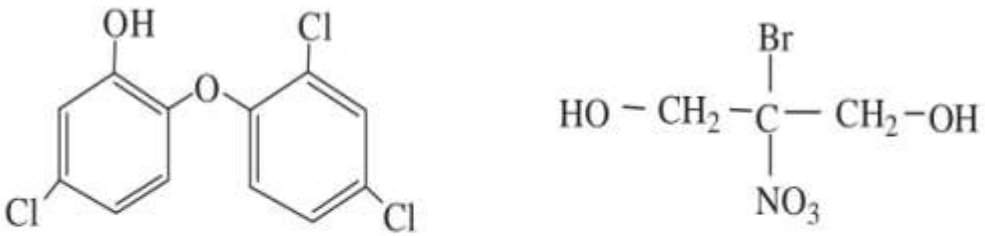


Fig. 5. The representation of the relationship between a) the adhesion of mouse embryonic fibroblast cells Vs WCA with an exponential model and b) the relationship between cell adhesion and surface roughness with a linear model. Adapted from Rezaei et al with permission from Elsevier. Copyright © 2015 Elsevier [26].

III. PLASMA SURFACE MODIFICATION OF POLY VINYL CHLORIDE :

Medical polymers are important in the treatment of diseases and have a direct consequence on patient's health. When medical polymers are implanted inside humans, they can become places for bacteria to adhere and breed [27]. Infection frequently results and is by far one of the major clinical complications. Prevention of device-related infection remains a major challenge to deliver quality medical care and the problem is causing a high rate of mortality and morbidity thereby significantly increasing health care costs [28]. To obtain anti-infective properties, medical polymers are usually impregnated or compounded with some antibacterial or antimicrobial reagents [29]. These technologies require large quantities of the antimicrobial reagents, typically on the order of a few g/m2 and the reagents are not immobilized on the surface. As a result, they are gradually released when these anti-infective polymers are embedded inside humans. One of the ways to tackle this problem is to control the physicochemical interactions between the bacteria and medical polymer surface [30].



Triclosan Bronopol

Fig. 1. Chemical structures of triclosan and bronopol.

Silver coatings, surface-immobilized polyethylene (PE) oxide, surface thiocyanation, and surface modification by various gas plasmas (such as oxygen and argon) have been suggested [31]. We propose here to use plasma immersion ion implantation (PIII) to conduct surface modification.

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In PIII, the specimens are surrounded by plasma and pulse-biased to a high negative potential relative to the chamber wall. Most biomedical devices have sophisticated shapes and irregular surfaces, and PIII is thus an excellent technique yielding good surface conformity and uniformity due to its non-line-of-sight characteristic [32]. Poly vinyl chloride (PVC) is one of the common medical polymers. Triclosan (2, 4, 4P-trichloro-2P-hydroxydiphenylether) and bronopol (2-bromo-2-nitropropane-1,3-diol) shown in Fig. 1are two types of compounds that exhibit immediate, persistent, broad-spectrum antimicrobial effectiveness as well as little toxicity in clinical use [33].

3.1 MATERIALS REQUIRED:

- Medical grade poly vinyl chloride
- Triclosan
- Bronopol
- Anti-bacterial test apparatus and reagents

3.2 EQUIPMENT USED:

- Plasma immersion ion implante

3.3 METHODS

3.3.1 Plasma modification:

The PVC samples with dimensions of 5 cm_5 cm_0.2 cm were made by injection molding machine. The samples were laid on stainless-steel substrates and inserted into the plasma immersion ion implanter [34]. The O2 plasma treatment was performed at the optimal conditions based on many trial experiments. After the initial plasma treatment, the samples were uniformly coated with the antibacterial reagent triclosan or bronopol in 20% alcohol. After the alcohol had volatilized, the samples were reloaded into the implanter and then underwent argon plasma ion bombardment to ensure that antibacterial reagent combined well with the PVC surface[35]. Again, these treatment conditions were based on trial experiments. Finally, the samples were washed three times using 70% ethanol to scour off loose triclosan or bronopol on the surface. The samples were treated using different types of processes to compare the antibacterial effectiveness [36].

3.3.2 Surface characterization:

In order to reduce errors, the method of subtraction between two spectra is adopted in this work using the following relationship,

AS =Ai _ fA0

where AS is the degree of absorption on modified layer, Ai and A0 are degrees of absorption before and after modification, and f is the coefficient related to the wavelength[37]. Photoelectron spectroscopy employing a monochromatic Al Ka radiation operated at 14 kV and 350W.Scanning electron microscopy (SEM) was used to study the surface of the samples. The surface hydrophilicity using distilled water as the medium was determined[38].

3.3.3 Anti-bacterial determination:

The antibacterial performance against Staphylococcus aureus (S. aureus, gram positive) and Escherichia coli (E. coli, gram negative) was determined by the method of plate-counting. The samples were first washed with 70% ethanol to kill any bacteria on the surface. After drying, a 0.2 ml solution of bacteria was added and the surface was covered by a PE film (4 cm_4 cm). At a relative humidity (RH) of higher than 90% and temperature of 1C, the samples were incubated for 24 h. Afterwards, they were thoroughly washed with 20 ml of a 0.87% NaCl solution. For observation, 0.2 or 0.02 ml of the washing solution was added onto different dishes containing the nutrient agar. After 24 h of incubation under similar conditions, the active bacteria were counted and the antibacterial effect was calculated[39].

3.3.4 Bacteria adhesion:

All four kinds of samples were sterilized by 70% ethanol and cut into 16 pieces of approximately 2.0 cm2. They were put in four different flasks containing a cell suspension . A control flask containing the cell suspension without the sample was also evaluated as the control. After they were kept for 20 h at room temperature, the samples were taken out and rinsed with a 0.87% NaCl solution. Thereafter, the adherent bacteria were detached from the samples in 10 ml of the same NaCl solution ultrasonically. The solution containing the bacteria was used to determine the viable counts [40].

3.4 RESULTS AND DISCUSSION:

The surface of most medical-grade PVC is hydrophobic. On the other hand, triclosan and bronopol are hydrophilic and easily crystallized. In order to coat the PVC samples with these two antibacterial materials, the PVC surface must be modified

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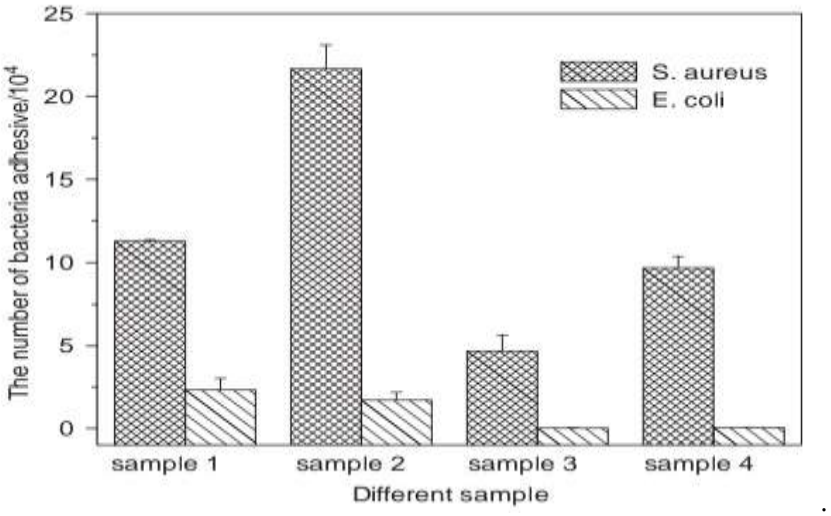

As shown in Fig. 6, the amount of S. aureus on all the samples is higher than that of E. coli. This is mainly due to the difference between the physicochemical characteristics of bacteria and materials such as bacterial hydrophobicity, bacterial surface charge, material surface chemical composition, and surface hydrophobicity.Nonetheless, the two kinds of bacteria exhibit a smaller degree of adherence onto samples 3 and 4 than samples1 and 2. In particular, a small amount of E. coli can be observed on sample 3 and 4. In our antibacterial experiments by plate counting, the modified samples exhibit higher antibacterial effects on S. aureus than E. coli. This may be due to the bacterial adhesion ability
and antibacterial effect that are common on the modified samples [41].

PURPOSE OF SURFACE MODIFICATION:

- Plasma treatment facilitates bonding of adhesives, coatings, epoxies and resins.
- Plasma treatment is used to alter the top few molecular layers of surface.
- When plasma is applied to the surface, the energy applied to the surface "activates" the surface.
- It is a process by which the surface polymer functional groups are replaced with different atoms from ions in the plasma to increase surface energy.
- The surface treatment of the implants are intended to generate a biologically active surface, which allow to improve the osseointegration between the implant and bone tissue [42].

SIDE EFFECTS OF PLASMA TREATMENT:

- Transfusion of plasma can lead to adverse reactions.
- Immune mediated reactions are most common – these include allergic and anaphylactic reactions.
- They can range in severity from mild to fatal.
- They have the unwanted effects of reducing some coagulation factors.
- Hemolytic transfusion reaction takes place [43].

ADVANTAGES OF PLASMA SURFACE MODIFICATION:

- Plasma processing provides interfacial energies and injected monomer fragments larger than comparable.
- Specific surface functionality without affecting the bulk.
- The limited penetration depth of such treatment provides vastly improved adhesion.
- These techniques have the capability to make an object hydrophilic.
- Inert material also takes place in surface modification.
- Very low unit cost per treatment [44].

LIMITATIONS OF PLASMA SURFACE MODIFICATION:

- Limited fluxes prevent high process rates.
- Several factors influence the efficacy of the flame treatment.

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- ❖ Difficult or impossible to coat inner surface of small diameter bores and other restricted access surfaces.
- ❖ Plasmas are thermodynamically unfavorable
- ❖ Therefore plasma processed surfaces lack uniformity [45].

ART

IV. CONCLUSION:

IN Implant related infections (IRI) is responsible for more than half of all hospital-acquired infections and is a burden for patients and health economies. IRI can be reduced or prevented by using biomaterials with antibacterial properties. Such biomaterials are obtained by modifying the surface of conventional biomaterials to bring in an antibacterial property. The main findings of this review can be listed as follows;

- ➢ S. aureus and E. coli are the most commonly investigated infection-causing agents for the determination of the antibacterial activity of the modified surfaces.
- ➢ The antibacterial activity of bactericidal surfaces that does not exhibit kill-and release mechanism should be monitored for more extended periods because dead bacteria can accumulate on the surface, reducing the surface's antibacterial activity and conditioning the surface for subsequent bacterial adhesion.
- ➢ Ag is predominantly used as the antibacterial agent and is incorporated into the surfaces by both direct and indirect plasma techniques.
- ➢ There is an increasing trend in inducing antibacterial property by decorating the surface of biomaterials with micro and nanostructures using plasma techniques.
- ➢ Plasma immersion ion implantation is demonstrated to be a viable method to modify the surface of medical poly vinyl chloride (PVC) to improve its anti-bacterial performance.
- ➢ The plasma modified PVC with Bronopol exhibits good anti-bacterial properties.
- ➢ The plasma modified PVC with Triclosan has better anti-bacterial performance against E.coli than Bronopol.
- ➢ The stability of the surface modification and the duration of the antibacterial activity should be tested for periods and environmental conditions relevant to the application area of the material of interest.

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