Plasma-based Surface Modification Applications of Biomaterials – A Review

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ABSTRACT

Plasma-surface modification method (PSMM) is an efficient and inexpensive surface processing method for various materials and has generated great interest in the field of biomedical engineering. This paper focuses on the numerous conventional plasma methods and experimental approaches applied to materials research for suitable biomedical applications, including plasma deposition, laser plasma deposition, plasma sputtering and etching, plasma polymerization, plasma spraying, plasma implantation, and so on. The distinctive benefit of plasma modification is its biocompatibility and surface properties can be enhanced on a selective basis while the bulk characteristics of the materials stay unaltered. Existing materials can hence be used and the requirement for new materials may be circumvented thereby reducing the time for the development of novel and efficient biomedical devices.

1. INTRODUCTION

Cold atmospheric pressure plasma (CAPP) processes (grafting, etching, deposition) have been extensively utilized for altering the surface properties of materials in various domains [1]. CAPP is also very efficient in the modification of surface properties of biomaterials [2] due to its versatile nature that enables it to effectively tailor physical /chemical characteristics of the surface materials at ambient temperature (25 °C) without affecting the majority of material properties [3]. Excellent adaptability, no use of solvents, minimum consumption of reagents, and effortless blending in current industrial processes are additional benefits of this CAPP processing method. Specifically, surface modification of biomaterials and devices operating at low pressure (LP) has a prolonged tradition in comparison to atmospheric pressure plasma technology. Additionally, the properties of surfaces can be selectively altered using the plasma-based surface modification method (PSMM to improve the performance of the biomaterials. For example, by modifying the functionality of the surface using thin film deposition, the optimal physical/chemical/surface properties can be achieved [4-9].

Plasma-based techniques combine the benefits of ion beam technologies and conventional plasma acts as an efficient method for medical implants involving intricate shapes [10]. Also, alteration of the surface energies of the materials can enhance the adhesion strength, biocompatibility, and coating and surface properties [11]. Though AP plasmas have been studied for surface engineering of biomaterials, they quite recently made an entry in this field.

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AP plasmas have been examined for their potential application in processes such as decontamination /sterilization [12] as well as in plasma medicine (i.e., the medicinal application of cold plasmas in the medical field) [13].

Concisely speaking, plasma-based methods present the following advantages concerning the engineering of these biomaterials [12-13]. (a) The advantages of plasma processing occur from the profound knowledge of plasma chemistry and physics understood from several technological applications, e.g.- microelectronics [14]. (b) Plasma-based surface modification method is reproducible, consistent, comparatively low-cost, and relevant to different complex geometries and a diverse range of materials such as composite, polymers, ceramics, and metals. [15–17]. (c) Treatments employing plasma can cause variations in a variety of surface attributes, which include, biological, tribological, mechanical, chemical, electrical, and optical properties [18]. (d) Plasma processing methods are coherent with various masking methods to allow surface patterning [19, 20], this process is extensively implemented in industries such as microelectronics. (e) Plasma treatment provides decontaminated surfaces and can be scaled up to commercial production comparatively easily. Whereas the adaptability of non-plasma methods for several substrate materials is lesser [21]. Hence, the plasma-surface modification method (PSMM) proved to be a cost-effective and efficient materials processing method that has attracted a lot of attention in biomedical engineering. It is possible to change the chemical composition and properties such as chemical inertness, refractive index, metal adhesion, lubricity, dyeability, wettability and biocompatibility of materials surfaces using PSMM [9- 11].

Orthodontic devices, venous catheters, and surgical instruments are treated with PSMM to enhance fretting resistance, friction, and biocompatibility. Dental implants and orthopedic hips need bone adhesion control, which is accomplished on Ti alloy surface done by implantation of Ca^{+} ion and the non-thrombogenicity required for artificial blood vessels is accomplished via endothelial cell adhesion control on polymeric surface implemented using ion implantation. [22]. PSMM of biomaterials is an interesting field, and a review of presently existing approaches, and modification systems have extensive applications in the biomedical field.

Among the various PSMM techniques, plasma immersion ion implantation and deposition (PIID) are an extensively used method that can execute various processes, such as simultaneous implantation, etching, and deposition as it combines the merits of ion beam technologies and conventional plasma.

2. PRINCIPLE OF PLASMA IMMERSION ION IMPLANTATION AND DEPOSITION (PIID)

Plasma consists of electrons, excited particles, and ions with electromagnetic radiation. The most essential characteristic of plasma is that both negative and positively charged particles maintain charge equilibrium, and the collective sum of the negative and positive charges in an adequately huge volume is 0. For generating plasma, ionization or separation of electrons from molecules or atoms in the gaseous state is essential. In most real-world settings, the plasma is generated via electrical discharge. Normally, a PIID system contains a high-voltage pulse modulator, a workpiece stage with a vacuum chamber, and a plasma source.

For the duration of the PIID processing, the substrate (workpiece) is submerged in plasma generated via high voltage bias, this causes electrons to be pushed away from the substrate and also simultaneously pushes the positively charged ions towards it thereby generating a plasma sheath surrounding the substrate. Plasma sheath accomplishes a pivotal role in PIID since it determines the process of implantation and the same is applied to predict parameters associated with the process (implantation dose implantation current) [23]. Positive ions are spread up by the electric field resulting in vertical implantation into the negative potential surfaces, as demonstrated in Fig.1.

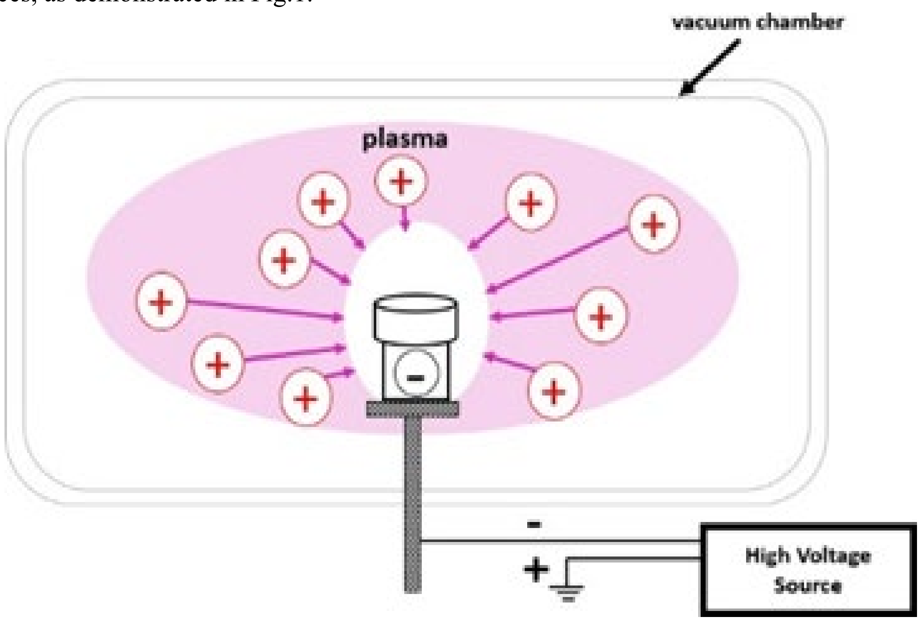

Fig.1. Mechanism of plasma immersion ion implantation and deposition

As the substrate is shielded by the plasma sheath, PIID is predominantly utilized in operating devices involving intricate shapes. Nevertheless, insulating samples are subjected to high negative potential as a consequence of which there is a charging effect of the dielectric surface due to which full applied bias potential is not attained by the insulator surface, which subsequently results in the plasma sheath being irregular. The impacts of charging are primarily defined by the dielectric coefficient, pulse frequency, pulse duration, and sample thickness. But, for insulators, the deformation is usually because of heat generated via collisions between ions in the PIID process is observed significantly than for conductors due to their extremely poor thermal conductivity [23].

The essential difference between traditional ‘line of sight’ ion implantation and PIID is that, in PIID, the substrate is immersed in the plasma directly and supplied with high negative potential that functions as the system’s active part, whereas, in the conventional ion implantation process, there is separation of substrate from the ion beam generation. Modifications of numerous metals, for example, magnesium and aluminum alloys, titanium and titanium alloys, and polymers have been done to improve the bioactivity, antibacterial activity, biocompatibility, and mechanical properties [23-26].

3. PLASMA SHEATH DYNAMICS

The plot of time evolution of the transient plasma sheath defines the distribution of energy of implanted ions and implantation current which determines the surface modification efficiency of the PIID process. So, when a high-voltage negative potential (rectangular pulse) is supplied to a substrate submerged in plasma, it results in ion sheath development across the surface of the substrate. Subsequently, ions are pushed in the direction of the substrate surface, where they are implanted. The dynamics of plasma sheath are now clearly defined, it has been comprehensively examined for various geometries which include, planar, spherical/cylindrical, in the case of both non-collisional [27-29] and collisional sheaths [30]. By physical timescales, there are three different stages of plasma sheath development [31]. Initially, if there is the instantaneous application of bias voltage, then on a timescale of the inverse electron plasma frequency electrons are then repelled exposing a matrix of ions, that are too heavy to react immediately: thus an "ion matrix sheath" develops,

$$w_{pe}^{-1} = \left(\frac{\epsilon_0 m_e}{n_e e^2}\right)^{\frac{1}{2}} \tag{1}$$

where, ϵ is the permittivity of free space, n_e and m_e are the density and mass of electrons.

Secondly, on the slower timescale of the inverse ion plasma frequency, the index denotes i to ions, and Q^- is the charge state number of mean ion, whose value is 1 for most if not all plasmas,

$$w_{pe}^{-1} = \left(\frac{\epsilon_0 m_e}{n_i (Q^- e)^2}\right)^{\frac{1}{2}} \tag{2}$$

The energy distribution of the ions in the initial transitional phase relies on their initial position in the ion matrix sheath. Plasma ions approaching the edge of the plasma sheath (the boundary between plasma and sheath) are driven by the sheath's field and consequently extracted from within the plasma. Consequently, the sheath edge shifts away from the biased surface, i.e., the thickness of the sheath expands [31]. Finally, on an extended time scale, typically tens of w_{pi}^{-1}, the density of current & the sheath progress approaches a steady state. The negative pulse duration is generally lasting longer than w_{pi}^{-1} therefore it can be considered that the thickness of sheath at steady-state is determined by the steady-state Child-Langmuir law,

$$g = \frac{2^{\frac{5}{2}} \epsilon_0 V_0^{\frac{3}{4}}}{3 \exp\left(-\frac{1}{4}\right) e^{\frac{1}{4}} n_e^{\frac{1}{4}} (kT_e)^{\frac{1}{4}}} \approx \lambda_{De} \left(\frac{eV_0}{kT_e}\right)^{\frac{3}{4}} \tag{3}$$

here substrate is supplied with negative potential throughout the pulse (as an approximation, the plasma potential can be presumed to be equivalent to the ground potential), k is the Boltzmann constant, T_e is electron temperature, g is independent of the ion mass, does not depend much on the temperature of electron and is inversely proportional to the square root of the density of plasma and λ_{De} is the electron Debye length [31].

4. PLASMA FOR BIOMEDICAL APPLICATIONS

Cold atmospheric pressure plasma (CAPP) techniques are widely employed to alter the properties of the surface of different materials and further stimulate programmed reactions from biological media, cells, proteins, and tissues connected to these surfaces, (in vivo/in vitro), Fine-tuned hydrophilic/hydrophobicity [24], immobilized biomolecules [25], programmed diffusion of chemically functional groups, (e.g., bioreactor membranes[26]), non-fouling characteristics[26] and antibacterial properties (e.g., bandages[32]), are few of the necessary surface properties desired for several biomedical applications, these properties can be transferred to biomedical devices & biomaterials. Numerous efforts are being made to build CAPP based on dielectric barrier discharge (DBD), due to their ability to operate in mild conditions and atmospheric pressure and their capability to generate plasmas in portable volumes, such plasma discharges can prove to be valuable tools meant for membranes and biomaterials [33].

Hydrophobic coatings have been deposited by atmospheric pressure-based dielectric barrier discharge (AP-DBDs) fed with chlorine /fluorine-based organic precursors [34] and with $C_6H_{18}O_3Si_3$ (hexamethylcyclotrisiloxane) [35]. These films have extensive applications for biomedical applications [33-35] and in the design of chemical sensors [36], this domain area requires control of the adhesion and wettability.

Furthermore, DBD-based CAPP systems are widely employed in the deposition of hydrophilic coating functionalized with polar groups which not only enhance the growth of cells and adhesion process but further deliver chemical groups required for immobilization of biomolecules (saccharides, peptides) applied in numerous biomedical applications that include providing a natural combination of biomolecules (where cells can multiply in living tissues) and mirroring of Extra Cellular Matrix [37]. It is a proven fact, for example, organic coatings enriched with nitrogen encourage both cell differentiation and adhesion of mesenchymal stem cells [38]. Marasescu et al. [39] examined atmospheric-pressure plasma and low-pressure plasma sources co-polymerizations by employing dual gas mixtures of N2, NH_3, and C_2H_4, respectively, they were examined for deposition of plasma polymer coatings enriched with nitrogen for biomedical applications. The author analyzed surface characteristics and deposition kinetics of plasma polymerized ethylene rich in nitrogen (PPE:N), PPE:N, coatings were studied as concerning the gas mixture ratio, $X = NH_3(N_2)/C_2H_4$ to understand the physiochemical properties of coatings as well as the total nitrogen concentrations to be employed for biomedical applications. Girard et al. [40] employed a pilot-scale dielectric barrier discharge (DBD) reactor for the deposition of polymerised thin film material on various substrates. Further, Rino et al. [41] examined plasma polymerisation of acrylic acid using DBD-based atmospheric pressure plasma (APP). Wherein the impact of operational parameters (discharge power and monomer concentration) on the properties of the deposited films had been examined. They found that deposition parameters should be appropriately considered to safeguard the stability of coatings with high carboxylic acid densities Ward et al. [42] proved that a highly functionalized plasma polymer layer can be rapidly deposited using ultrasonic atomization of acrylic acid. The results of this research work were verified using material characterization methods such as Fourier transform infrared spectroscopy (FTIR) and X-ray photoelectron spectroscopy (XPS) spectroscopies that indicated that polymerization occurs predominantly via the C=C bond. Poly (acrylic acid) known for its wettability also has good gas barrier and adhesive properties. Furthermore, Nisol et al. [43] employed Radiofrequency (RF) based atmospheric pressure plasma to deposit plasma-polymerized poly (ethylene glycol) films on substrate gold surfaces and polyvinylfluoride (PVF) using gaseous or liquid Tetra ethylene glycol dimethyl ether ($CH_3O(CH_2CH_2O)_4CH_3$) as precursor. The results of their experiment revealed good biocompatibility in correlation to surface composition. Recently, PSMM techniques such as plasma immersion ion implantation and deposition, plasma polymerization, and plasma spray, have been proven to be effective and economical. These methods have been successfully implemented in the biomedical industry [44-46]. The PIID & D method was developed to avoid the line-of-sight restriction in conventional beam-line ion implantation. Another major benefit of PIID is the wide-ranging processing ability to modify the surface properties of various biomaterials, including polymers, metals, and ceramics, and the PIID technique can introduce a variety of different classes of functional groups and elements into the complex shape materials [47,48]. Furthermore, the other distinctive benefit of plasma-based surface modification in comparison with the other methods is that it's selectively capable of improving the properties of surfaces (approx. 100 nm), whereas the bulk contributions remain unchanged [44-49].

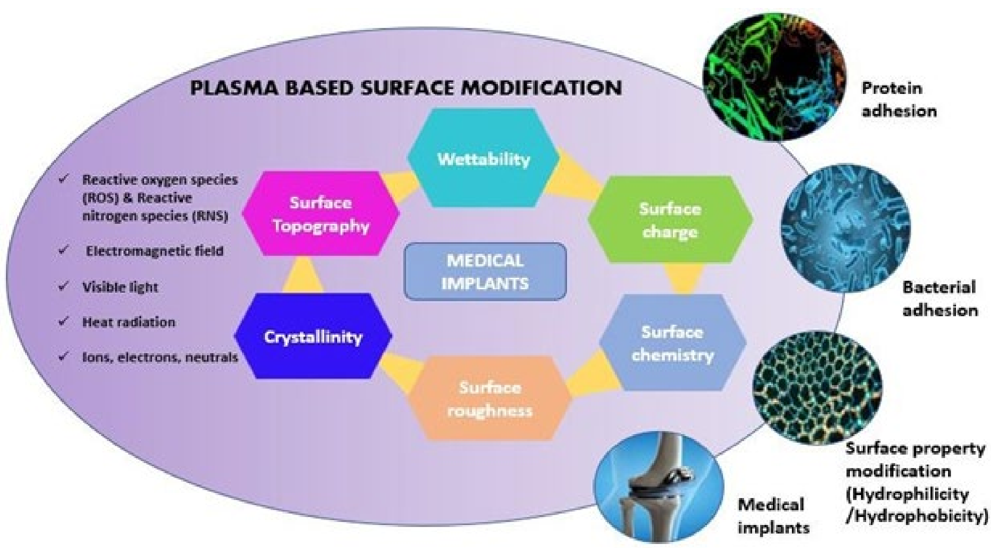

Fig.2. Overview of plasma-based surface modification applications

In recent years PIID technique has also been successfully implemented in biomedical implant modification due to its versatility and controllability [50]. M Cisterna et al. [51] examined the implantation of nitrogen ions into Ti substrate using PIID technique in a capacitively coupled radio frequency plasma. Their results proved that The ion implantation increases the load-bearing ability of Ti surface by the formation of α-Ti(N) and δ-TiN phases on the sub-surface of Ti, and maintains the biocompatibility of Ti surface. Mandl et al. [52] employed oxygen for the PIID process for titanium alloys leading to the formation of a rutile surface layer on small rods, that were injected into rat femurs to assess osseointegration and biocompatible properties. Furthermore, there are also some polymers favored materials that have greater biocompatibility properties owing to their effortlessness of molding, corrosion resistance, density comparable to tissue, machining & high fracture toughness. Plasma immersion ion implantation processing of polymer surfaces has been implemented to acquire the necessary characteristics for interface with cells and tissues [53]. Han et al. [54] found that that PIID treatment using oxygen is extensively utilized to hydrophilize various polymer-based surfaces, and thus PIID processing is an efficient approach using oxygen plasma and pulsed bias of the sample holder. The authors [54] found that oxygen implantation (5 kV, 10 s pulses, 500 Hz, 5 min) was viable for all samples of polyethylene, polystyrene, polycarbonate, silicone rubber, poly (ethylene naphthalene), poly (ethylene terephthalate), and poly (vinyl chloride). They found that the contact angle reduced to 2°. McKenzie et al. [55] examined the modification of the polymer poly (aryl ether ketone) (PEEK) using the PIID process to enhance its performance for biomedical applications. The authors subjected the polymer samples to different plasmas of hydrogen, argon, oxygen, and deuterium by placing them on a substrate holder which was subjected to 10 and 15 kV and 15 µs pulse. McKenzie et al. [55] found argon based PIID modification reduced the contact angle to half that of the untreated material whilst PIID treatment employing oxygen reduced the contact with water drops to approximately zero. Deeper treatment is essential for ensuring the longer time needed for regaining the hydrophobic character. Their results also indicated that treatment using hydrogen delivered the deepest modification and further electrical resistivity was observed to be highest for treated material using oxygen as compared to argon and hydrogen PIID treatment.

Recently many smart materials have also been employed as implant materials, one of the most extensively examined materials is poly-urethane shape memory polymers (SMPU). A few major issues with SMPU include bio-inertness and hydrophobicity. Xingying et al. [56] applied the PIID technique to enhance and enable one-step covalent and surface wettability, and functionalization of SMPU with biological molecules to produce a tunable and biocompatible surface. Their experimental results proved that PIID treatment increased the wettability of smart materials (SMPU), induced the lowest acute inflammatory response in vivo, and improved host biocompatibility in vivo. There is another polymer Ultrahigh molecular weight polyethylene (UHMWPE) that has been extensively employed in medical implants due to its inherent properties such as excellent wear resistance when coupled with smooth Co-Cr-Mo alloy or austenitic stainless-steel surfaces in vivo and low friction. It is imperative to understand that the important constraint that determines the longevity of the medical implants is the body’s response to the UHMPWE [57]. Therefore, there is a compulsive need to improve the wear resistance of UHMWPE & hence, lower the wear debris volume, this consequently would promote implant loosening, this is a timely task from both a technological and scientific viewpoint. Furthermore, nitrogen ion implantation of UHMWPE has been demonstrated to enhance its tribological properties in terms of extremely low friction and low wear rate [58]. Despite the use of numerous polymer types for bioimplants, metallic materials inherently play a vital role in biomedical application materials for bone, vascular, or dental implants due to their fracture toughness and high mechanical strength [59]. Among the numerous metallic materials treated using PIID employed in biomedical applications, Titanium (Ti) and its alloys have received significant attention for biomedical applications in various branches of dentistry and medicine due to its lightweight, exceptional biocompatibility, excellent corrosion resistance, and outstanding balance of mechanical properties. Ti and its alloys are mainly implemented for implant devices as a replacement for failed hard tissue, for e.g. bone plates, artificial hip joints, artificial knee joints, dental implants, etc. Titanium & its alloys have their application in dental products such as crowns, dentures, and bridges mainly manufactured via the precision casting method [60]. Ti-based alloys manufactured using PIID have been extensively employed for dental applications due to their excellent biocompatibility [61,62].

Table: 1 Plasma strategies used for the generation of antibacterial surfaces for biomaterials

Ref	Plasma system	Substrate	Precursors/process gases	Biocompatibility	Remarks
63	PIII	Mg–Ca	oxygen	no cytotoxic effects could be observed from the MC3T3- E1 cells	biodegradable Mg–Ca and Mg–Sr alloys with a plasma-modified surface show good potential as orthopedic implants
64	PEO	Ti	Electrolyte composition: $C_4H_6CaO_4$, $C_3H_7CaO_6P$ and $Na_2[B_4O_5(OH)_4]\cdot 8H_2O$	Live bacteria coverage reduced	Non-cytotoxic to adipose Derived stem cells
65	PECV D	Fluorapatite glass-ceramic disks	CH_4 and SiH_4	Less than 20% of surface coverage in polymicrobial biofilm	Non-cytotoxic to human periodontal ligament fibroblast
66	PEO	Additively manufactured Ti-6Al-4V	Electrolyte composition: $C_4H_6CaO_4$, $C_3H_7CaO_6P$, and AgNPs	Antibacterial activity of Ag containing PEO Samples and containing Ag + hydrothermally treated samples	Non-cytotoxic to preosteoblast MC3T3-E1 cells, improved cell proliferation
67	PEO	Ti	$CH_3CHOHCO_2)2Ca$(0.15 M) NaH_2PO_4 (0.09 M)	Release killing Contact killing	Fluorescence staining Analysis (Better cellular proliferation on (Ti-10Cu) coating

The Ti-6Al-4V alloy is a biocompatible alloy implemented for dental prostheses. Huang et al. [68] analyzed the effectiveness of nitrogen-based PIID treatment of Ti-6Al-4V alloy for improving biological responses that include antibacterial adhesion, and cell growth and to enhance its corrosion resistance as seen in Fig.3. They used the oral bacteria Streptococcus salivarius to assess antibacterial adhesion, that includes morphology and bacterial attachment. Their experimental results indicated that the proposed nitrogen-based PIID treatment enhanced the corrosion resistance of Ti-6Al-4V alloy, while also enhancing antibacterial adhesion and cell responses necessary for dental applications. In the past few years, PIID technology has been regarded as an efficient and simple technique to produce a protective covering on medical implants especially orthopedic implants to slow down the wear process.

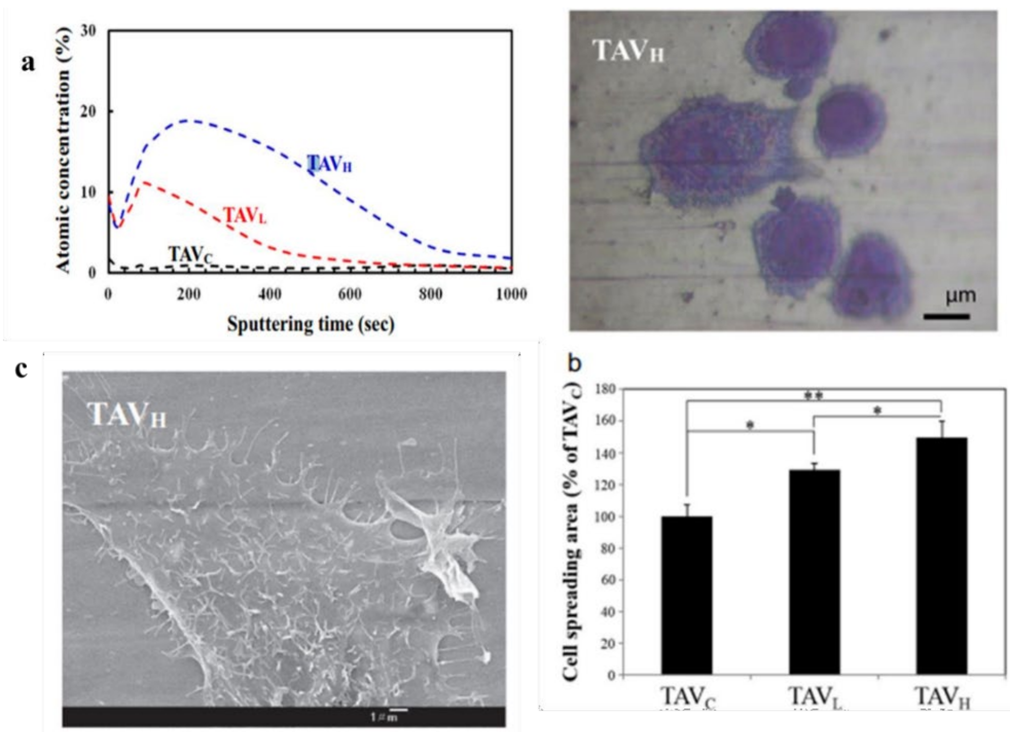

Fig. 3. (a) XPS depth profile analysis of the outermost surface of Ti-6Al-4V specimens before and after N-PIII treatment; (b) Crystal violet staining micrographs of hMSCs after 1 h of incubation on Ti-6Al-4V surfaces before and after N-PIII treatments; (c) FE-SEM micrographs of the attached hMSCs on the test Ti-6Al-4V specimens after 48 h of cell incubation [68]

Alonso et al. [69] designed Ti-6Al-4V implanted with nitrogen (N2) via PIID, and their results indicated that loadbearing capacity is dependent extensively on the implantation dose of N2 instead of the hardness and no noticeable hardening was seen after PIID treatment. Further, the function of O2 in N2 implantation has been investigated by Wan et al. [70]. They prepared Titanium nitride (TiN) and TiN /Titanium oxide (Ti-O) gradient films into Ti-6Al-4V via single implantation of N2 and in sequence dual ion implantation of N2/O2, respectively. The experimental results of Wang et al. [70] showed that the TiN/Ti-O coated sample exhibited the best wear performance in comparison to TiN-coated & untreated samples. Despite Ti-based biomaterials being employed extensively for biomedical applications due to their excellent fatigue strength, and formability, there are some major issues such as comparatively poor bioactivity which puts stringent limits on the long-term application [71]. To address this issue implantation of several elements have been done using PIID technology to improve the bioactivity of these Ti-based biomaterials. It is generally recognized that the OH (hydroxyl groups) on the exterior layer of biomaterials, such as Zr–OH , Ti– OH, Ta–OH , and Si–OH, have the potential to generate a negatively charged surface when immersed in simulated body fluid (SBF), thus producing bone-like apatite formation [72]. This apatite layer provides exceptional bone-bonding capacity for biomaterials inside the human body. Hence, generating a OH layer on the Ti alloy surface is an efficient approach to enrich its bioactivity [73]. Though traditional treatment methods of heat treatment and NaOH a comparatively much simpler mechanisms to create Ti–OH groups found on the surface, there is a great hazard of damage to the passive layer after the chemical etching process. PIID process is established as an excellent tool for plasma implantation without disturbing the bulk properties of the biomaterial. Hasan et al.[74] reported that anisotropic nanostructures created on the Ti surface exhibit high antibacterial activity against P. aeruginosa and E. coli (Fig. 4). The nanostructures resembled nanopillars and in addition, the attachment and proliferation of human mesenchymal stem cells were enhanced, and osteogenic differentiation was induced.

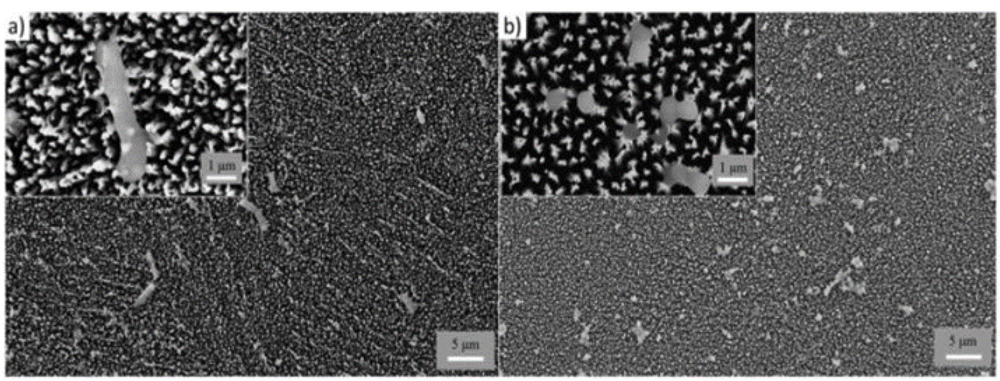

Fig.4. The anisotropic nanostructures created on the Ti surface exhibit antibacterial activity by disturbing the cell wall of a) P. aeruginosa and b) E. coli.[74]

Xie et al. [75] implemented H2O and subsequent H2 implantation processes into the Ti surface via the PIID process for generating a highly active surface consisting of Ti-OH groups [75]. Liu et al. [76] implanted H2 into the plasma-sprayed TiO2 surface coating to generate a Ti–OH- functionalized titanium surface. During this PIID process, the reaction between the outermost bridge oxygen species and energetic H2 ions significantly resulted in the establishment of Ti– OH bondings. Furthermore, the TiO2 coating acts as a H2 diffusion barrier. Thus, building Ti alloy-based bioactive surfaces with rich Ti–OH groups can be attained by a blend of H2 implantation and numerous oxygen-containing films on Ti-based alloy.

5. CHALLENGES IN BIOMATERIALS

Corrosion is one of the most significant challenges for a metallic implant. After implantation, corrosion happens when the metallic implant is inserted inside a living tissue via an electrochemical mechanism. Corrosion is important to understand since it can adversely impact the mechanical properties and biocompatibility. There is also clinical proof that the corrosion products released (metal ions and corroded particles) from the implants resulted in adverse biological reactions, and this further accelerated the corrosion process [76]. Various researchers have reported that PIID technology has been successfully implemented for the modification of biomaterial surfaces to improve their corrosion resistance [77-80]. Nickel–titanium (Ni–Ti) alloys have been extensively used as orthopaedic biomaterials due to their shape memory properties and superelastic properties. In these Ni-Ti alloys, there is a major issue of associated outward propagation of toxic nickel ions during extensive use within the human body generates a risk factor [77]. Ray et al. [77] implemented the PIID method for effecting a series of surface modifications to enhance the whole corrosion resistance using PIID. Their results gave a profound understanding of factors responsible for the anti-corrosion effectiveness of barrier layers, which includes composition & film quality as well as process parameters. Poon et al. [78] examined the anti-corrosion effectiveness of oxide films generated by oxygen-PIID (O2-PIID) and atmospheric pressure oxidation (O2-oxidation). Their results proved that the O2- PIID sample exhibited the best corrosion resistance than the O2-oxidation sample. PIID technique has also proved to enhance the biological properties responsible for protein adsorption, integration of tissues, differentiation, and adhesion of cells to establish biocompatibility. These biological properties are directly connected to the roughness of implant surfaces, wettability, and chemical composition. Ceramic coatings also offer exceptional bioactivity, however, the relatively weak bonding strength between coatings and substrates remains the main issue, which is due to the mismatch of thermal expansion coefficients. PIID technology can effectively solve this issue by producing in situ coatings on the surface of the material without affecting its bulk properties [79].

Infections caused by bacteria have been identified as one of the major obstacles during implant surgery, which might cause failure of implant, and revision surgery all linked with very high medical costs [80]. The solution to this issue is to produce biomaterials with antibacterial properties by incorporating a wide range of bactericidal agents into surfaces or changing surface physico-chemical characteristics for prevention of bacterial adhesion/growth [81-82]. Cold plasma jets could be generated at atmospheric pressure for biomedical applications via various electrode configurations [83-90]. As well-established wide spectra of antimicrobial agents, copper (Cu) and silver (Ag) had been implanted into several materials surfaces using PIID for offering brilliant antibacterial properties [91]. Liu et al.[91] proposed a new antibacterial mechanism for nano-particle embedded Ti via single PIID treated Ag. It is proved that Ti and Ag comprise of one micro galvanic couple due to various potentials when submerged in an electrolytic solution. The cathodic reaction generates a region (depleted of the proton) between the titanium substrate and bacterial membrane, which interrupts the production of adenosine triphosphate and kills the microbe (bacteria). It is important to note that the multiplication of bacteria is reduced considerably on the Ag-PIID-Ti surface whereas that of osteoblasts is accelerated [91].

Hongqing Feng et al. [92] studied plasma and ion-beam modification of metallic biomaterials for improved anti-bacterial properties. Plasma and ion-beam surface modification produces favorable biological effects in titanium-based and magnesium-based materials such as antibacterial activity and biocompatibility. Silver ion implantation endows titanium and titania with good bactericidal characteristics without compromising the growth, proliferation, and osteogenesis of osteoblasts, and sometimes even improves these biological properties.

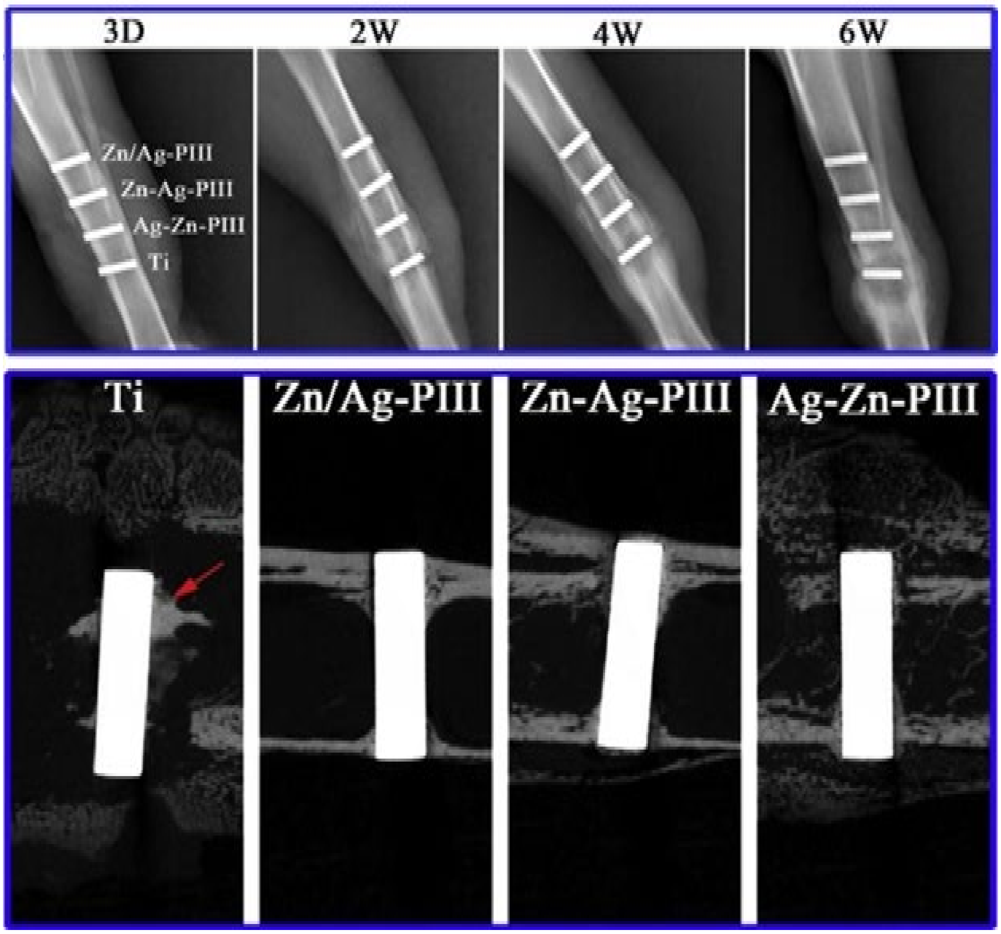

Fig.5. The micro-CT scans were obtained 6 weeks after surgery [92].

Zhang et al. [93] performed a sequence of Cu or Ag ion implantations to examine the antibacterial capability of polyethylene surfaces. Their investigation revealed that either Cu - /Ag - implanted polyethylene sample (Cu-PIID-PE or Ag-PIID-PE) can provide exceptional antibacterial activity instantaneously due to the release of Cu or Ag ions. Further studies by Zhang et al. [94] revealed that several gases like N_2, O_2, and NH_3, co-implanted with Cu into PE surfaces stimulated higher antibacterial activity and slower release of Cu ions in comparison to Cu- PIID-PE, suggesting improvement in prolonged antibacterial performance. A similar result was obtained for N2/Ag co-implanted sample [95]. Chemical investigations revealed that the plasma-based implantation employing gas caused dehydrogenation and created unsaturated, $-C = N - C \equiv N$, $C = C -$ & $C = O$, bonds, which are considered to be capacity for regulating the release rate of Ag or Cu and generate a considerable effect on killing bacteria. In particular more $-C \equiv N$ & $- C = N$ bonds in N2/Cu co-implanted using PIID are the most successful in extending the antibacterial properties. The function of unsaturated bonds in establishing antibacterial activity has been proven by a recent study done by Wang et al. [96], in which N2 plasma-modified PBSu exhibited effective antibacterial activity for both Escherichia coli and Staphylococcus aureus along with the antibacterial ratio of 91.41 % and 90.34%. In another investigation, Wang et al. [97] generated 3 thin a-C: H films with different chemical bonds & structures on polyethylene terephthalate (PET) using C2H2 PIID at variable pressures (0.5, 1 and 2 Pa). The adhesion tests showed that comparable bacterial adhesion efficacies between Staphylococcus epidermidis on the film deposited at 1.0 Pa, which was found to be 1/6th of those bacteria on the surface of untreated PET and S. aureus on the a- C : H film deposited at 0.5 Pa. The bacterial reduction can be justified utilizing adhesion due to free energy (ΔFadh), which is found to be positive for strains of bacteria on the PET surfaces fabricated at a working pressure of 0.5 and 1.0 Pa. (ΔFadh > 0), signifying energetically unsuitable for these surfaces. Other than free energy theory, the author suggested with decreasing sp3/sp2, the bacterial population adhered to the carbon film reduced and further found that the adhesion of bacteria on a-C :H films seemed related to the film structure. Another major issue associated with biomaterials is that any enhancement of antibacterial properties is always coupled with diminished biocompatibility that doesn't meet the clinical requirements. To address this problem, a deeper understanding of biophysiochemical interactions and comprehensive investigations of the implant-bio interface are essential to achieve characteristic bacteria / eukaryotic cell-responsive surfaces.

6. CONCLUSION

PSMM has developed into a widely employed physical process technique appropriate for implementing surface modification of different materials. Specifically, PIID offers a wide-ranging processing ability to modify the surface properties of several biomaterials by incorporating a multitude of various kinds of functional groups and elements into various materials. This analysis has reviewed recent progress and development of mechanical and biological properties of biomaterials (Ti, Ti alloys, and biopolymers) by plasma-based surface modification processes. The review indicated that other than the chemical and physical properties and composition, the microstructure and nanostructure of biomaterial surfaces have been determined as a pivotal element influencing different types of cellular responses, for eg. cell adhesion, differentiation, and morphology. However, the generation of adaptable micro- or nanostructures cannot be accomplished using only PIID technology. It is imperative to ensure the optimal performance of biomedical implants along with the compatibility requirements of biological molecules, a blend of PIID with additional fabrication methods might be vital. Furthermore, interdisciplinary methods will be a prerequisite for design and fabrication of biomaterial surfaces

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