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Application of Low-Temperature Plasma Processes for Biomaterials

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1. Introduction

Physical plasma is defined as a gas in which part of the particles that make up the matter are present in ionized form. This is achieved by heating a gas leading to dissociation of the molecular bonds and subsequently ionization of the free atoms. Thereby, plasma consists of positively and negatively charged ions and negatively charged electrons as well as radicals, neutral and excited atoms and molecules (Raizer, 1997; Conrads and Schmidt, 2000). On the one hand, plasma is a natural phenomenon as more than 90 % of the universe is in the plasma state, for example in fire, in the polar aurora borealis and perhaps most importantly in the nuclear fusion reactions of the sun. On the other hand, plasma can be created artificially and has found applications in technology like plasma screens or light sources. The use of high temperature plasma for energy production is still the focus of ongoing research.

For the modification of biomaterial surfaces, low temperature plasma which is sometimes also called cold plasma is used. It is characterized by a low degree of ionization at low or atmospheric pressure (Roth, 1995; Roth 2001; Hippler et al., 2008). To create low temperature plasmas, a compound is first transformed into a gas and then ionized by applying energy in the form of heat, direct or alternating electric current, radiation or laser light. Commonly used plasma gas sources are oxygen, nitrogen, hydrogen or argon. Two typical research plasma reactors for different applications are shown in Fig. 1. Depending on the nature and amount of energy, low temperature plasmas are characterized by a non-equilibrium between electron temperature and gas temperature. Thus the main parameters which define the characteristics of a plasma and thereby its applicability are its temperatures, types and densities of radicals and its level of ionization. In material science, possible applications of low-temperature plasmas include the modification of surface properties like electrochemical charge or amount of oxidation as well as attachment or modification of surface-bound chemical groups. Consequently, properties like hardness, resistance to chemical corrosion or physical abrasion, wettability, the water absorption capacity as well as the affinity toward

specific molecules can be modulated specifically and precisely by the use of low-temperature plasmas (Meichsner et al., 2011).

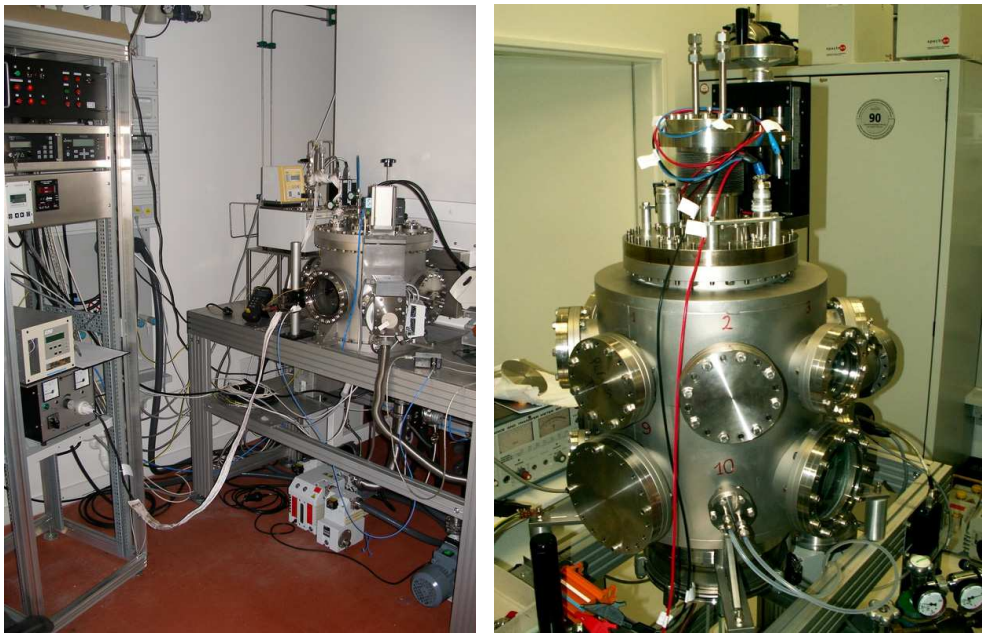

Fig. 1. Laboratory-size low-temperature plasma reactors for argon / ethylenediamine plasma (left) and pulsed magnetron sputtering (right)

Plasma treatments can be used to improve different aspects of the therapeutic characteristics of medical implants (Ohl & Schröder, 2008; Schröder et al., 2011). Possible applications include the incorporation of therapeutic agents into implants or the attachment of drug molecules onto the material surface. This includes for example plasma processes used for surface coupling of antibiotic substances or for integration of metal ions into biomaterial surfaces to create implants which exhibit long-lasting antibacterial properties after implantation. By creating such implants with antibacterial properties, the often devastating effects of implant-related infections could be markedly reduced. Therapeutic agents for other applications can be loaded onto implant surfaces via plasma treatment as well to achieve their controlled release over time. Possible applications are drug-eluting stents and vascular prostheses which release drugs to reduce blood coagulation and thombosis as well as to prevent intima hyperplasia and restenosis.

Low-temperature plasma-modified surfaces were furthermore found to possess specific bioactive properties in vitro and in vivo. For example, such surfaces influence the attachment and growth of osteoblasts, fibroblasts and inflammatory cells which provides the possibility to enhance implant ingrowth and tissue regeneration as well as to reduce implant-related inflammation, thereby improving the biocompatibility. Another field of application is plasma sterilization of prosthetic materials which is a gentle approach that can be adapted for many different materials and which is especially advantageous over

conventional methods regarding the required time. From a process technology point of view, sterilization would also be a beneficial concomitant effect of other plasma treatments aimed at modulating specific material properties. The range of materials which can be treated with low-temperature plasma processes includes many materials with an established track record in regenerative medicine, for example ceramics like hydroxyapatite, polymeric materials like polyester, polypropylene, silicone and polytetrafluoroethylene, and metals like titanium, titanium-based alloys and steel. Consequently, the possible utilization of plasma treatments in the field of biomaterials includes a wide range of applications in cardiovascular and reconstructive surgery, orthopaedics and dentistry. Therefore, low-temperature plasma processes have great potential for improvement of medical implants. In the following, a concise overview of the respective applications and the underlying plasma processes is presented, putting an emphasis on recent developments. The main directions of research in this developing field are reviewed in terms of the respective aims, the relevant materials and the potential clinical applications.

2. Plasma-assisted creation of implants containing therapeutic compounds

The coating of implant surfaces with therapeutic agents is an interesting approach to improve the clinical outcome of implantation. In this field, the treatment with plasma can be used to either facilitate the surface attachment of the respective drug itself or to create a layer on top of a coating with a therapeutic compound to modulate the kinetics of its release. Among the multitude of possible applications, recent research activities are focused on two main directions: the equipment of implants with antibiotics and other compounds with antibacterial properties to prevent implant-related infections and the coating with anti-thrombogenic agents to prevent the formation of blood clots and thrombosis for implants with blood contact like vascular prostheses and stents. In principle, most of the plasma-based approaches used in these areas could also be applied with other drugs which have already been examined for drug-eluting implants, for example paclitaxel and everolimus (Butt et al., 2009), dexamethasone (Radke et al., 2004) or trapidil, probucol and cilostazol (Douglas, 2007) all aimed at reducing restenosis after implantation of vascular stents which is an emerging and clinically promising field for controlled drug release in biomaterials research.

2.1 Implant surfaces with antibacterial properties

The equipment of implants with antibacterial properties can be achieved either by attaching antibiotic substances or by creating surfaces which release metal ions which are known to have anti-infective effects. Polyvinylchloride, a polymer which is used for endotracheal tubes and catheters, was equipped with triclosan and bronopol, compounds with immediate and persistent broad-spectrum antimicrobial effects, after the surface was activated with oxygen plasma to produce more hydrophilic groups for effective coating (Zhang et al., 2006). Experiments using *Staphylococcus aureus* and *Escherichia coli* demonstrated the effectiveness of these surfaces. Similarly, polyvinylidenfluoride used for hernia meshes was modified by plasma-induced graft polymerization of acrylic acid with subsequent binding of the antibiotic gentamycin (Junge et al., 2005). In addition to the microbiological examination of the gentamycin-releasing material, the in vitro and in vivo biocompatibility was examined by cytotoxicity testing and implantation into Sprague-Dawley rats for up to 90 days, and no side effects on biocompatibility were observed. The fact that an implant

coating with a sustained release of gentamycin is effective against bacteria with no adverse effects on cellular proliferation was also confirmed by the evaluation of titanium implants with gentamycin grafted onto the surface of a plasma sprayed wollastonite coating (Li et al., 2008). Wollastonite was previously found to be a promising material for bone tissue repair due to its high bonding strength to titanium substrates, its mechanical properties and its bioactivity and biocompatibility (Liu et al., 2008).

Due to their well-known antibacterial effects, metals like silver, copper or tin are possible alternatives to classical antibiotic compounds as an effective and sustained release from coatings is possibly easier to achieve due to their small size. Similarly to gentamycin as mentioned before, silver has been used as a powder added to a plasma-sprayed wollastonite coating on titanium implants (Li et al., 2009). In comparison to a coating without silver, tests with *Escherichia coli* confirmed the antibacterial activity of the silver while an examination of osteoblast morphology revealed no obvious difference between both coatings. Furthermore, the release of silver was also examined for amino-hydrocarbon plasma polymer coatings (Lischer et al., 2011), after plasma immersion ion implantation into polyethylene (Zhang et al., 2008) and for silver nanoparticles bound to an allylamine plasma polymer thin film (Vasilev et al., 2010b). Similarly, the use of copper for antibacterial implant coatings has also been studied by plasma implantation into polyethylene (Zhang et al., 2007). The use of plasma immersion ion implantation is however not restricted to polymer materials as demonstrated by recent work on the application of this process for equipment of titantium surfaces with copper ions (Polak el al., 2010). Compared to controls, the implants created by this Plasma immersion ion implantation of copper reduced the number of methicillin-resistant *Staphylococcus aureus* cultivated on the respective surfaces (Schröder et al., 2010a). Ion implantation can also be used for non-metals like fluorine which is of particular relevance for dental applications. This was examined with titanium, stainless steel and polymethyl methacrylate for fluorine alone (Nurhaerani et al., 2006) or with stainless steel for a combination of fluorine with silver (Shinonaga & Arita, 2009).

2.2 Implant surfaces with reduced thrombogenicity

Another field of interest for plasma applications is the coating of implants with anti-thrombogenic agents. This is of special importance for vascular prostheses and stents which are in constant contact with blood. For these implants, thrombosis and blood clot formation are severe and potentially life-threatening complications. Classical anti-coagulants used for thrombosis prophylaxis and treatment include coumarin derivates like phenprocoumon for oral application as well as heparin which is physiologically found in the body and extracted for medicinal use from mucosal tissues of slaughtered meat animals and hirudin, originally from the European medical leech *Hirudo medicinalis*, for parenteral use. The Plasma-based attachment of heparin has for example been examined for stainless steel which is used in stents (Yang et al., 2010). For this application, a pulsed-plasma polymeric allylamine film with a high amino group density was created to subsequently immobilize heparin via its carboxylic groups and established coupling chemistry using 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide and N-Hydroxysuccinimide. In a similar way, a heparin coating of polystyrene surfaces was achieved by preadsorption with undecylenic acid, a FDA-approved natural fungicide for skin disorders, followed by treatment with argon plasma and covalent immobilization of an albumin-heparin conjugate (van Delden et

al., 1997). Another example is the heparinization of polyurethane by low temperature plasma and grafting of poly(acrylic acid), water-soluble chitosan and heparin (Lin et al., 2005). In addition to well-established anti-coagulants, the endothelial membrane protein thrombomodulin, a co-factor in the thrombin-activated anticoagulant pathway, has also been examined regarding plasma-based attachment on biomaterial surfaces. This application was studied for polytetrafluoroethylene, a common material for vascular prostheses, via CO_2 plasma activation and subsequent vapour phase graft polymerization of acrylic acid (Vasilets et al., 1997; Sperling et al., 1997). Another surface modification which was examined for reduced thrombogenicity was plasma-induced graft polymerization of 2-methacryloyloxyethyl phosphorylcholine on titanium alloy surfaces which resulted in reduced deposition and activation of platelets in subsequent in vitro experiments with ovine blood (Ye et al., 2009).

2.3 Regulation of drug release by barrier layers

In addition to plasma-assisted surface attachment of therapeutic compounds, plasma processes can also be used to create an over-coating which acts as a barrier to regulate the drug release. This application has for example been examined using daunomycin, an antibiotic substance, and rapamycin, a compound with immunosuppressive and anti-proliferative effects which is used for example in stents to prevent excessive tissue growth, in combination with a plasma polymerized tetramethylcyclo-tetrasiloxane coating (Osaki et al., 2011). Changing the deposition time length resulted in different coating thickness which, like the molecular weight of the drug, was found to influence the drug-release rate. A comparable approach was used on polyetherurethane onto which a plasma-deposited poly(butyl methyacrylate) membrane with controlled porosity was applied to control the release of ciprofloxacin (Hendricks et al., 2000). Adhesion and colonization of *Pseudomonas aeruginosa* was evaluated to assess the antimicriobial effectiveness.

Furthermore, an over-coating can also be applied to surfaces which release metal ions. For instance, the antibacterial surfaces created by plasma immersion ion implantation of copper as mentioned before were also treated with an additional layer of plasma-polymerized allylamine to regulate the Cu release and to modulate cellular adhesion and spreading. This combination reduced the antibacterial effects of the surface to some extent but did not completely disable it (Schröder et al., 2010a). On the other hand, the combined treatment also led to lower local inflammatory reactions after implantation into rats (Schlosser, unpublished data), highlighting the need to find an optimal balance between in vivo biocompatibility and sufficient antibacterial effects. Another study demonstrated that creation of thin films by plasma polymerization for controlled release of silver ions and traditional antibiotics is applicable to the surface of many different medical devices (Vasilev et al., 2010a).

The use of an over-coating to regulate the release rate is not only possible for antibiotics but also for antithrombogenic agents. This has for example been studied for hirudin for which an additional layer of 2-hydroxyethyl methacrylate created by glow discharge plasma deposition on drug-loaded polyurethane matrices served as a diffusional barrier controlling the hirudin release kinetics depending on the plasma coating conditions (Kim et al., 1998).

Of more general interest for the field of drug-releasing implants is a recent study which describes the use of liposomes, artificial vesicles enclosed by a lipid bilayer. Liposomes can

be used as drug containers by encapsulation of therapeutic compounds, in some cases additionally targeted to their site of action by antibodies, and potentially offer a wide range of applications. Covalent coating of liposomes onto stainless steel was achieved via radiofrequency glow plasma assisted creation of a thin film of acrylic acid characterized by surface carboxylic groups to which the liposomes were attached via formation of amide bonds (Mourtas et al., 2011). While the study was considered by the authors to be a proof of principle, the presented method seems to be a versatile approach due to possible changes of process parameters for the liposome immobilization procedure as well as regarding the choice of different drugs for encapsulation.

3. Plasma-based surface functionalization

Medical implants interact with their surrounding tissue in a complex manner. For example, a so called neointima layer is formed over time at the inner surface of vascular prostheses. Bone implants based on calcium phosphate possess osteoconductive and osteoinductive properties. Most importantly, all biomaterials are foreign to the body and the aim of acute and chronic inflammatory reactions which can persist for as long as the implant remains in the body. While short-term temporary implants which are removed some time after implantation should rather be inert, long-term implants intended for permanent presence in the recipient's body should ideally possess bioactive properties to facilitate proper tissue integration. A multitude of different approaches has been examined with the aim to influence the interactions between biomaterials and the host tissue, for example by regulation of protein and cell attachment to improve the implant ingrowth and to reduce implant-related inflammation. Possible methods include for example the coating with different proteins, with biomembrane-derived phospholipids, with diamond-like carbon or ceramics or the attachment of chemical groups to create surfaces with a specific electric charge. Low-temperature plasmas have extensively been examined in vitro and in vivo for these applications.

3.1 Creation of bioactive surfaces

The cell-material and tissue-material interactions can be influenced by modifying the surface charge via chemical groups. For example, an enhanced osteoblast growth in vitro was observed for surfaces modified with plasma-polymerized 1-aminoheptane (Zhao et al., 2011). The plasma-based deposition of acetaldehyde and allylamine polymer coatings on silicon and perfluorinated poly(ethylene-co-propylene) was found to influence the outgrowth of bovine corneal epithelial tissue for up to 21 days (Thissen et al., 2006). A treatment of Titanium samples with a comparable process called plasma-polymerized allylamine, based on the polymerization of allylamine after activation with a continuous wave oxygen-plasma, creates a positively charged amino group rich surface aimed at improving attachment of the negatively charged matrix substance hyaluronan. This coating was found to be advantageous concerning initial osteoblast adhesion and spreading (Nebe et al., 2007) and to have beneficial effects in vitro on the formation of focal adhesions as well as on cell morphology and spreading (Finke et al., 2007) and vinculin mobility (Rebl et al., 2010) of osteoblasts. An in vivo examination in rats revealed no negative influence on the number of total and tissue macrophages, T cells and MHC class II antigen-presenting cells in the peri-implant tissue (Hoene et al., 2010). Furtheremore, it was demonstrated that the

plasma parameters influence the surface properties and thereby the host response. Samples with a lower plasma duty cycle (ratio of plasma on-time t_{on} divided by the overall pulse duration $t_{on} + t_{off}$) resulted in a higher layer thickness and protein absorption as well as a lower oxygen uptake due to sonication in distilled water. Consequently, the hydrogel-like character of the plasma-polymerized allylamine films was probably more developed for the high duty cycle samples, resulting in an overall lower inflammatory response in vivo than for the implants created with a low duty cycle (Hoene et al., 2010). Similar results regarding enhanced cell adhesion were also obtained for a plasma consisting of a mixture of argon and ethylenediamine (Finke et al., 2011). A treatment of a hip prosthesis with this plasma process is exemplarily shown in Fig. 2.

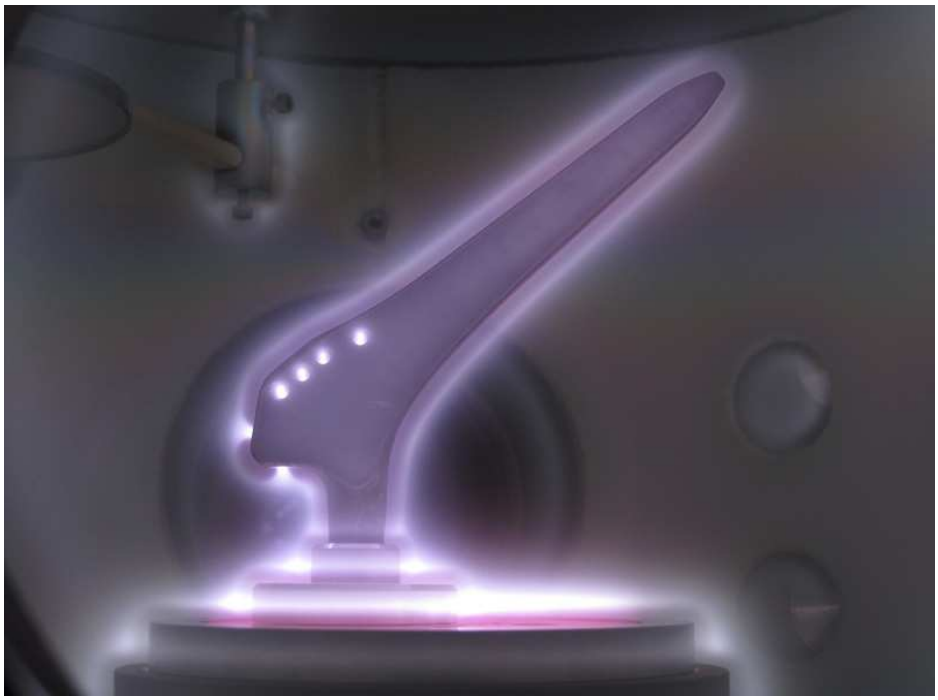

Fig. 2. Hip joint implant in low pressure plasma using a mixture of argon and ethylenediamine for cell adhesive coating

In contrast to these positively charged NH_2 films, a coating of Titanium implants with acrylic acid after similar plasma activation, called plasma-polymerized acrylic acid, results in a negatively charged COOH-group rich surface which was found to facilitate osteogenic differentiation by stimulation of mRNA expression of early (ALP, COL, Runx2) as well as late (BSP, OCN) bone differentiation markers (Schröder et al., 2010b). However, the long-term inflammatory response in vivo caused by this coating were increased compared to uncoated controls (Schröder et al., 2010b), highlighting the difficult balance that improving one specific aspect of implant characteristics is often accompanied by adverse changes in other parameters. Furthermore, it illustrates the problem that the results of in vitro experiments on the one hand and in vivo studies on the other are often inconsistent due to

the complex nature of reactions in a living organism which can only partially and often inadequately be modelled using in vitro approaches.
Similar to metals and metal alloys, cell attachment on polymers can also be modulated by plasma treatment. The application of glow-discharge plasma of mixed ammonia and oxygen on polytetrafluoroethylene surfaces reduced the hydrophobicity and increased the attachment of aorta endothelial cells (Chen et al., 2003). Furthermore, an oxygen plasma has been shown to improve surface attachment of mouse fibroblasts L-929 on thermoplastic polyetherurethane used for gastric implants (Schlicht et al., 2010).
Low-temperature plasma can also be used to achieve immobilization of bioactive molecules. This was demonstrated for example by an oxygen plasma treatment to enhance the immobilization of simvastatin, which stimulates bone formation, onto Ti surfaces (Yoshinari et al., 2006). The deposition of thin film from ethylene plasma on Ti surfaces allows the chemical attachment of hydroxyethylmethacrylate onto Ti to improve the in vitro adhesion of mouse fibroblasts L-929 (Morra & Cassinelli, 1997). Albumin nanoparticles conjugated with a truncated fragment of fibronectin were directly patterned onto polymers to elicit adhesion and spreading of human mesenchymal stem cells and fibroblasts (Rossi et al., 2010). Stable coating of collagen type I onto two different metal alloys (Ti6Al4V, X2CrNiMo18) was achieved using a argon-hydrogen plasma and found to increase the viability and attachment of human osteoblast-like osteosarcoma cells SAOS-2 (Hauser et al., 2010), and coating of collagen onto silicone performed with an argon-oxygen plasma led to increased adhesion and viability of mouse fibroblasts 3T3 (Hauser et al., 2009). Poly(lactide-co-glycolide), a biodegradable polymer widely used as scaffold material for tissue engineering, was modified by oxygen plasma treatment followed by anchorage of cationized gelatine for improved attachment and growth of mouse fibroblasts 3T3 (Shen et al, 2007).
A popular material for bioactive coatings on implants for bone replacement is calcium phosphate which is the main natural component in the bone matrix where it accounts for more than half of the bone weight. It exists in a variety of different chemical preparations differing in their atomic and ionic lattice configuration, their Ca:P ratio, the number and size of pores, and their surface area. One calcium phosphate preparation commonly used for biomaterials is hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) which is generally considered to be osteoconductive and osteoinductive (Walschus et al., 2009). Using a process called plasma spraying, it is possible to deposit thin and dense layers of hydroxyapatite onto metal implant surfaces (de Groot et al., 1987). Due to the well-established bioactive properties and good biocompatibility of hydroxyapatite, these coatings have been clinically used in dentistry and orthopedics since the mid 1980s (Tang et al., 2010). Furthermore, plasma spraying can also be used to create other layers like Ca-Si-Ti-based sphene ceramics (Wu et al., 2009), hydroxyapatite/ silica ceramics (Morks 2008), zirconia (Morks & Kobayashi 2008; Wang et al., 2010), yttria-stabilized zirconia (Wang et al., 2009) or hydroxyapatite/ yttria/ zirconia composites (Chang et al., 1997; Gu et al., 2004). One important advantage of plasma-sprayed coatings for biomaterials is the ability to precisely modify the microstructure by modulating the parameters of the plasma process (Khor et al., 2004; Huang et al., 2010) to study and improve microstructure-related tissue growth stimulation.

3.2 Plasma-assisted vapour deposition of inert diamond-like carbon layers

Another field of increasing interest which should be mentioned briefly in this chapter is the plasma-based coating of implants with diamond-like carbon for which plasma-assisted chemical vapour deposition is the most commonly used deposition method. Diamond-like

carbon layers can exhibit the typical diamond crystalline structure, an amorphous structure or a mixture of both (Schlosser & Ziegler, 1997). Furthermore, depending on the coating procedure, they can consist of pure carbon or contain other elements. Overall, diamond-like carbon films are characterized by an excellent mechanical stability and hardness, a high corrosion resistance as well as reduced tissue-material interactions and no detectable cytotoxicity (Schlosser & Ziegler, 1997). Particularly for implants where inertness of the surface is required, they are therefore an attractive option for coating of medical implants in a number of applications in reconstructive surgery and dentistry (Roy & Lee, 2007). Diamond-like carbon coatings have for example been examined for ureteral stents (Laube et al., 2007), orthodontic archwires (Kobayashi et al., 2007), joint implants (Thorwarth et al., 2010) or cardiovascular stents (De Scheerder et al., 2000).

4. Plasma sterilization

Sterilization as the elimination of living microorganisms like bacteria, viruses and fungi, especially pathogenic agents, is an important aspect in biomaterials applications to prevent implant-related infections. Commonly used methods to achieve sterility include the treatment with heat, chemicals and irradiation. Each of those methods has its specific disadvantages and not all are equally usable for the sterilization of medical implants. For example, a heat treatment can lead to irreversible modifications of heat-labile materials and to denaturation of protein coatings. Irradiation with UV or gamma rays requires cost-intensive equipment with high safety requirements and can also cause irreversible modifications of proteins such as albumin and collagen used as sealing impregnation of vascular prostheses, as well as biomaterials like polymers. Chemical sterilization using for example ethylene oxide could result in residuals on the treated surface. Therefore, the application of low-temperature plasma processes as an alternative sterilization technique which is a gentle process from a physico-chemical point of view has been the focus of ongoing research since several years. It is known that exposure to plasma effectively and irreversibly damages cells from different bacteria species like for example *Escherichia coli, Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus cereus* or *Bacillus subtilis* (Bazaka et al., 2011). Especially for modified or functionalized biomaterials, sterilization with low-temperature plasma would therefore be an attractive option as it could be achieved as a secondary effect of plasma treatment aimed at other surface modification purposes (Bazaka et al., 2011).

The application of plasma sterilization of heat-sensitive silicone implants has recently been demonstrated (Hauser et al., 2011). Similarly, sterilization of poly-L-lactide electrospun microfibers which can be used to repair tissue defects can effectively be achieved by hydrogen peroxide gas plasma which ensures sterility of the scaffolds and does not affect their chemical and morphological features (Rainer et al., 2010). Biodegradable polyester three-dimensional tissue engineering scaffolds which are particularly prone to morphological degeneration by high temperature and pressure were successfully sterilized with an argon-based radio-frequency glow discharge plasma (Holy et al., 2001), demonstrating the usefulness of plasma sterilization for damageable materials. Similar results were also obtained for starch based biomaterials for which a recent study found that treatment with oxygen plasma resulted in more hydrophilic surfaces compared to UV-irradiation (Pashkuleva et al., 2010). Furthermore, both methods gave comparable results regarding osteoblast adherence, from which the authors concluded that plasma sterilization

as well as UV-irradiation improved the biocompatibility and can be used as cost-effective methods for sterilization.
For metal implants, it was found that rapid and efficient sterilization of different alloys like X2CrNiMo18-15-3, Ti6Al7Nb und Ti6Al4V is possible with plasmas based on different gas mixtures such as argon/oxygen, argon/hydrogen and argon/nitrogen (Hauser et al., 2008). Sterilization of non-woven polyethylene terephthalate fiber structures for vascular grafts with either ethylene oxide or low temperature plasma resulted in comparable fibroblastic viability but a significantly higher TNF-α release, indicating activation of macrophages, for macrophages incubated on the fibres which were treated with ethylene oxide (Dimitrievska et al., 2011). Subcutaneous implantation into mice demonstrated inflammation accompanied by a foreign body reaction with no difference after 30 days between the samples treated with the two sterilization methods. A comparison of the effects of sterilization with gamma irradiation, ethylene oxide treatment, electron beam irradiation and plasma sterilization on the in vitro behaviour of polylactide fibres revealed that sterilization with both gamma and electron beam irradiation caused a decrease of the intrinsic viscosity while treatment with ethylene oxide and plasma sterilization had no pronounced effects on the sample properties (Nuutinen et al., 2002). These results also highlight the potential of plasma sterilization as a gentle alternative to other commonly used sterilization methods. However, it is not equally suitable for all materials as it might have adverse effects on relevant material properties. For example, demineralized bone matrix which was sterilized with low-temperature gas-plasma sterilization lost its osteoinductive capacity (Ferreira et al., 2001).
Another application related to sterilization is the removal of surface contaminations. This is particularly important for residues like prion proteins which have contagious and pathogenic properties. The usefulness of plasma treatment for molecular-level removal of proteinaceous contamination was recently demonstrated for silicon and surgical stainless steel surfaces (Banerjee et al., 2010).

5. Conclusions and outlook

Low temperature plasmas offer a wide range of applications in biomaterials research to improve the clinical performance of medical implants by modifying their surface characteristics. In many cases, the use of plasmas facilitates modifications which are difficult or unable to achieve by conventional physical or chemical methods, like for example the stable attachment of molecules onto noble metal surfaces. The concise overview presented in this chapter demonstrates the potential of low temperature plasma processes for the precise modification of specific implant surface properties while retaining the overall characteristics of the material. The main aims of research in this field are to reduce implant-related complications like infections, thrombus formation and inflammation as well as to modulate the cell-material and tissue-material interactions for improved implant ingrowth. Another equally important area of research is the use of plasmas for sterilization. The studies which were presented here indicate that plasma processes are applicable for practically all commonly used biomaterials including metals, polymers, ceramics and composites, offering a wide range of clinical applications in all fields of reconstructive medicine.
Given the versatility of low temperature plasma processes and the diverse nature of materials and clinical applications, it is difficult to predict future developments in this field. If there is any specific trend, then it is an increase in the number of studies which deal with biodegradable materials, reflecting an overall surge of interest in biomaterials research for this kind of materials. Another development is the use of increasingly sophisticated methods for surface analysis, making it possible to draw precise conclusions regarding relationships

between process parameters, surface characteristics and the biological response. Two important aspects in need of more research are on the one hand the aging-related surface changes of plasma-modified biomaterials and on the other hand their in vivo behaviour. Most of the studies discussed here used only in vitro methods to assess the biocompatibility. However, for the step from the lab into clinical practice it is essential to examine the in vivo biocompatibility by using appropriate animal models. There are several aspects of biocompatibility, both short- and long-term, which can not be adequately examined with in vitro methods like cell culture techniques. More detailed in vivo testing together with a better understanding of the influence of the plasma parameters on the physico-chemical material properties and on the response of cells, tissues and living organisms will ultimately turn currently promising research projects into clinical applications for improved implants. The increasing interest in the application of low-temperature plasmas in biomaterials science is illustrated by the formation of long-term and large-scale research projects, scientific centers and institutional networks in recent years, for example the Plasma Physics and Radiation Technology Cluster at the Eindhoven University of Technology in the Netherlands, the Center for Advanced Plasma Surface Technology (CAPST) in Korea, and the Campus PlasmaMed at the Leibniz Institute of Plasma Science and Technology Greifswald, the University of Greifswald and the University of Rostock in Germany.

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