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Trends in surface engineering of biomaterials: atmospheric pressure plasma deposition of coatings for biomedical applications

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Abstract

Cold plasma processes for surface engineering of biomaterials and biomedical devices are traditionally performed at low pressure; more and more, though, surface modification plasma processes at atmospheric pressure are also gaining popularity. This short review is aimed to list briefly atmospheric pressure plasma processes reported, in the last decade, for adapting the surface of materials to the best interactions with cells, bacteria and biomolecules.

1. Cold plasmas for Life Sciences

Cold plasma processes (deposition, grafting, etching) are widely used for modifying the surface of materials in several fields [1]. They look highly attractive also for modifying the surface of biomaterials, being versatile tools to tailor smartly chemical/physical properties of material surfaces at room temperature, without altering their bulk. High versatility, minimum consumption of reagents, no use of solvents, high/easy integration in existing industrial processes are other advantages of the technique. In surface engineering of biomaterials and devices low pressure (LP) have a longer tradition than atmospheric pressure (AP) plasma processes [2- 9]. However, also AP plasmas are being investigated for surface engineering of biomaterials, as we will show in the text, but they entered recently in this field. AP plasmas are intensely investigated for other recent applications of plasmas for Life Sciences such as sterilization/decontamination [10] and Plasma Medicine (i.e., the therapeutic use of cold plasmas in medicine) [11].

2. Atmospheric Pressure cold plasmas for material processing

Beside the widespread use of corona discharges in air to impart hydrophilic, polar character to polymers [12, 13], whether and when AP cold plasmas will become competitive with respect to LP systems for material processing, and reach their same versatility and variety of deposition, grafting and etching processes on different materials, is still an open questions. In AP Dielectric Barrier Discharges (DBD), for example, the strong influence of the substrate on the processes and the narrow inter-electrode gap are significant drawbacks [14]. Despite this, DBDs find promising applications in material processing [15]. Even though DBDs are well known since about one century, mostly used in traditional applications like ozone generation and pollution control [15, 16], they have been applied only in the recent past to thin film deposition and material treatments [14, 17, 18]. Despite the well-established knowledge of LP processes, the interest toward DBDs is growing up, mostly because they can, in principle, operate without pumping systems, even though control of the working atmosphere would often be desirable. Some experimental configurations of AP-DBDs are sketched in Figure 1, characterized by at least one insulating layer in the current path between the metal electrodes. DBD configurations are also used in plasma jet [19].

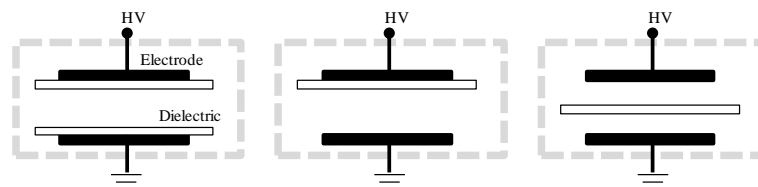


Figure 1- Typical parallel electrodes DBD configurations

The configuration with both electrodes covered with a dielectric is mostly used for plasma deposition (PE-CVD) of thin films. Typical inter-electrode gaps are in the range 1-5 mm depending on the substrates, the process, and the gas feed. The characteristic voltage range required to ignite the AP-DBD is between few hundred to several thousand volts. Typical frequencies are in the range 50 Hz - 500 kHz [15]. From the material processing point of view, the most important feature is that the electrical regime of the discharge is well-controlled and reproducible. Since electrical conditions are

highly substrate-dependent, AP processes may be more difficult to optimize with respect to LP counterparts [14]. The macro/micro roughness of the substrate and its electrical properties could strongly influence the whole deposition process. DBDs can operate in two main regimes, namely: filamentary, characterized by narrow and short-living micro-discharges; and homogeneous, in which the filaments are not observed. In case of the filamentary regime, micro-discharges have to be homogeneously distributed in time and space into the discharge gap, to avoid stationary filaments that could damage the growing coating or/and the substrate itself. Under defined frequency/voltage conditions, and defined range of parameters, to be optimized in each reactor, homogeneous discharges can be obtained, obviously most desirable in material processing for their homogeneity, as in LP plasmas. The gas feed, in particular, plays a crucial role; the presence of additives in the plasma gas (He, Ar, or N₂), in fact, can promote the transition from homogeneous to filamentary; for this reason DBD PE-CVD processes occur in the filamentary regime most of the times.

3. DBD deposition processes for biomedical applications

LP plasma techniques are extensively used to tailor the surface properties of materials and to elicit pre determined responses from proteins, cells, tissues and biological media in contact with them, *in vitro* and *in vivo*. Tuned hydrophilic/phobic character, pre-determined distribution of chemical functional groups, immobilized biomolecules (e.g., for Tissue Engineering scaffolds and bioreactor membranes), non fouling characteristics (e.g., for Intra Ocular Lenses), patterned micrometric domains (e.g., for lab-on-chip platforms), resistance to bacterial colonization (e.g., for prostheses and bandages), lubricity (e.g., for catheters) are some of the desirable surface properties for different biomedical applications, that can be imparted with LP plasmas to biomaterials and biomedical devices. Other relevant properties to be optimized in this framework are the adhesion of the coatings to the various substrates, and their stability (no leach of moieties, no delamination) in water and biological media. Several efforts are being exerted to develop also AP cold plasma processes based on DBDs, but also on plasma jets, for the same purpose. Due to operation at atmospheric pressure and mild conditions (e.g., absence of ion bombardment), and to their ability to ignite plasmas in small volumes, such discharges can be useful instruments for processing biomedical, textiles and membranes, as well as the inside of small caliber catheters and of porous scaffolds [20]. Hydrophilic functional surfaces for cell growth and biomolecules immobilization, as well as micro patterned surfaces, non fouling protein/cell repulsive and anti-bacterial coatings can be obtained with AP plasma processes. Table 1 lists some recent relevant papers on AP PE-CVD surface engineering processes of biomedical interest.

Table 1- Recent papers on AP DBD for biomedical applications

Topic	Paper (see references)
Hydrophobic/Superhydrophobic coatings	[21] Borcia et al; [22] Kim et al.
Hydrophilic and cell adhesive coatings	[23] Marasescu et al, 2009; [24] Morent et al, 2009; [25] Ward et al, 2003.
Micro-patterning of surfaces	[26] Girard et al, 2005.
Non fouling coatings	[27] Nisol et al, 2010; [28] Da Ponte et al, 2011.
Antibacterial coatings	[29] Sarghini et al, 2011; [30] Zimmermann et al.
Immobilization of biomolecules	[31] Che et al, 2009; [32] Heyse et al, 2008.
Functionalization processes	[33] Gebner et al, 2004; [34] Sarra-Bournet et al, 2006; [35] Mix et al, 2009; [36] Hahnel et al, 2011.

Hydrophobic and super hydrophobic coatings have been deposited by means of AP DBDs fed with fluorine/chlorine organic precursors [21] and with hexamethylcyclotrisiloxane [22], respectively. Such films find broad applications for chemical sensors and for biomedical and biological purposes, field in which the control of the wettability and the adhesion is strongly required. AP-DBD systems are used to deposit hydrophilic coatings functionalized with polar groups able *per se* to improve adhesion and growth of cells, but provide also chemical anchor groups for the immobilization of biomolecules (e.g., peptides, saccharides, etc.) for a large number of applications, including the imitation of the Extra Cellular Matrix (ECM), the natural blend of biomolecules were cells proliferate in living tissues [37]. It is well known, for example, that nitrogen-rich organic coatings promote cell adhesion and differentiation of mesenchymal stem cells; Marasescu et al [23] have focused their investigations on plasma-deposited N-rich films obtained from C₂H₄/NH₃ or C₂H₄/N₂ gas mixtures in

LP (L-PPE:N) and AP DBD (H-PPE:N) systems, respectively. AP deposited PPE:N coatings were used by Girard et al [26] to produce surfaces with alternated micrometric cell-adhesive and cell-repulsive domains. Square PPE:N arrays were obtained through a micrometric polyimide mask. Cells (growth plate, articular chondrocytes and U937 macrophages) were found to adhere and proliferate on the PPE:N islands but not on the polymer (usually polypropylene) substrate. Similarly, acrylic acid (AA) vapour and AA aerosol were used by Morent et al [24] and by Ward et al [25], respectively, to AP plasma deposit coatings containing $-\text{COOH/R}$ groups to promote cells adhesion. In both cases, decreasing the input power and increasing the AA concentration resulted in a higher retention of the AA monomer structure in the deposited coatings, clearly shown by the increased amount of carboxylic groups revealed by X-rays photoelectron spectroscopy measurements. Recently Nisol et al [27] have published what we believe is the first paper on the deposition of PolyEthyleneOxide (PEO)-like non fouling coatings with an AP plasma system, with two different approaches, i.e. AP Plasma Liquid Deposition (AP-PLD) and AP Plasma Enhanced Chemical Vapours Depositions (AP-PECVD). LP Plasma deposited PEO-like coatings are known for their non fouling properties in water media against protein, cells and bacteria [4, 38, 39]. In the AP-PLD process, liquid $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_4\text{CH}_3$ (TEGDME) was sprayed on the substrate and then exposed to an Ar AP plasma torch. In the AP-PECVD process vapours of the same compound, generated in a heated bubbling system, were carried into the plasma region with argon. The effect of the applied power was investigated; in both cases it was found that, as it occurs in analogous LP processes, coatings highly retaining the structure of the monomer, characterized by non fouling, protein repelling behaviour, could be deposited only at low power. At high power the structure of the monomer was lost in the coating, as well as the related properties. We also have plasma deposited [28] PEO-like non fouling coatings using an AP-DBD system fed with the aerosol of TEGDME in He. In controlled conditions where condensation is avoided, feeding the monomer in form of aerosol would improve the retention of its structure in the coating as well as the deposition rate [40]. The effect of the TEGDME aerosol concentration was evaluated as a function of the total He flow, used as carrier and aerosol gas, and of the applied voltage. The ether content (PEO-character) of the coatings could be tuned between 50% (protein/cell-adhesive) and 70% (non fouling). In a similar AP-DBD system using the aerosol of a water D-L lactic acid (LA) solution in He or N_2 , we could deposit coatings of potential biodegradable properties [28]. Antibacterial surfaces were developed by Sarghini et al [29] with a two steps AP-DBD process: first, substrates were activated with a N_2 discharge; then a coating was deposited injecting the aerosol of an organic precursor in the plasma phase by the N_2 flow. The best antibacterial properties were achieved when a silicon compound with quaternary ammonium (3-(Trimethoxysilyl)-propyldimethyloctadecylammonium; ODAMO) was used in mild deposition condition. The coatings retained the long chain structure and the ammonium groups of the monomer, both fundamental for the antibiotic activity, tested against *Escherichia Coli* bacteria. The AP plasma deposition of silica-like coatings containing silver as antibacterial agent has been reported by Zimmermann et al [30]; in this case HexaMethylDiSilOxane (HMDSO) was used as monomer, and silver nanoparticles or silver nitrate solution were fed as nitrogen aerosol in an AP DC plasma torch system. Taking advantage of the easy integration of DBDs with aerosol precursors, and of mild plasma condition, Heyse et al [32] have developed a new, original ONE-STEP approach to embed biomolecules in plasma deposited coatings. The aerosol of a biomolecule, dispersed in a proper solution, and the organic precursor are both introduced in the discharge and the protein is directly included in the growing coating. The simultaneous introduction of the bioactive molecules and of the reactive organic precursor requires that the AP-DBD is ignited in very mild plasma condition, to limit the damage of the biomolecules. The presence and the homogeneous distribution of a fluorescent protein, allophycocyanin, in the resulting coatings was shown by means of fluorescence microscopy images. We believe that this new immobilization approach, with no similar examples yet in LP systems, has great chances to be used in practical applications.

4. Conclusions

Recently reported surface modification AP plasma processes for biomedical applications have been reviewed, including the deposition of antibacterial coatings, of non fouling coatings, and of coatings

with embedded biomolecules. We believe that these new PE-CVD processes will soon lead to new original surfaces for biomaterials and biomedical devices.

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