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Plasma-synthesised carbon-based coatings for cardiovascular applications

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Abstract

Current cardiovascular stent platforms interact poorly with the human vasculature and still rely on drug therapy to avoid early failure due to blood clotting. A drug-free coating technology that could fully integrate an implanted stent through a combination of hemocompatibility and differential regulation of endothelial cells and smooth muscle cells would present a clear advantage over existing clinical approaches. Plasma discharges have been used as a coating technology in a wide range of applications over the last decades. Carbon-based thin films prepared by different plasma deposition methods are usually regarded as biocompatible materials as they are able to prevent the adhesion and activation of platelets and preferentially promote the adsorption of albumin over fibrinogen. However, the available literature seldom addresses entirely the aspects of biocompatibility and the challenging mechanical demands of such materials for stent coating. Recent advances suggest that plasma enhanced chemical vapour deposition can be used to prepare carbon-based thin films that allow for the linker-free immobilization of bioactive molecules. If successfully applied to a stent these coatings could represent a step towards stent specific biofunctionalization. This review examines the feasibility of using plasma discharges for the synthesis of carbon-based biocompatible materials for cardiovascular implantable devices, particularly stents.

Keywords: Plasma deposition; Carbon coating; Functionalization; Biocompatibility; Cardiovascular; Stent

Contents

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1. Introduction

Every year more than 6 million people undergo surgery around the world for the insertion of medical implants such as hip and knees prostheses, pacemakers, heart valves and coronary stents [1,2]. In the US alone around 1 million orthopaedic implants are inserted annually for knee and hip replacements [3] and these numbers are expected to rapidly increase to around 3 million by the year 2030 [4]. The increasing life expectancy of the population elevates demands for medical implants with a superior life span that can resist corrosion and wear, especially in load bearing and blood and/or tissue contacting applications. Additionally, insertion of exogenous materials into the body triggers immune responses in the areas surrounding the implant which can compromise implant performance and even necessitate revision surgery for implant replacement or extraction. Novel surface technologies that could mediate interactions between the implant and the host to prevent adverse reactions would clearly benefit the biomedical devices industry. In particular, there is a great demand for a universal technology capable of producing tailored biofunctional interfaces to simultaneously address a number of specific tasks depending on the application. Modulation of the surface properties such as hemocompatibility, protein adsorption / immobilization, differential attachment, proliferation and differentiation of cells are highly desirable. This review investigates the potential of using plasma-based tools as a universal coating technology for implantable medical devices, with particular focus on coronary stents. The deposition of biofunctional surfaces on coronary stents is a particularly interesting and complex case study as it combines: (i) physical–chemical, (ii) mechanical, (iii) geometric, (iv) blood clotting and (v) cellular response considerations.

1.1. Current coronary stent platforms

The World Health Organization [5] estimates that cardiovascular diseases represent 30% of total deaths worldwide, with coronary heart complications, including atherosclerosis, leading the list with a total of 7.3 million deaths every year. The same organization predicts that these numbers will rise up to 8% within the next 15 years, exacerbating an already serious problem. In the last three decades, percutaneous coronary interventions became widely used in the treatment of cardiovascular diseases and have been established as the first-line technique for revascularization of the coronary arteries. Among implantable biomedical devices, coronary stents are now the dominant vascular implant in percutaneous coronary interventions [6] with around 800,000 stents implanted annually in the US alone [7]. Stents are expandable cylindrical meshes used to re-establish the normal blood flow in blocked atherosclerotic coronary arteries, resupplying ischemic tissue. However, despite their widespread use, current stent platforms have only sub-optimal biocompatibility, interacting poorly with vascular cells and promoting blood clot formation.

The first commercially available stent platform was based on metallic alloys such as stainless steel (SS). Despite the extraordinary results in reducing the rate of abrupt vessel closure, one of the major pitfalls of coronary angioplasty, post-procedure complications related to stent implantation started to arise. The most common was in-stent restenosis, triggered by an inflammatory response due to blood vessel intima injury during stent deployment. Damage to the endothelium led to the migration and over-proliferation of underlying smooth muscle cells (SMC), causing vessel re-narrowing in a process called neointimal hyperplasia [8]. In order to overcome the draw-backs of bare metal stents, drug eluting stents (DES) were introduced. DESs are grafted with layers of biodegradable [9–11] or non-biodegradable [12–14] polymers, in which a pharmacological agent is loaded and can be locally released within a given period of time. By incorporating anti-proliferative agents, drug-eluting stents were successful in inhibiting the over-proliferation of SMC, hence reducing the effects of hyperplasia. However, an unintended consequence of DES was a substantially increased risk of long-term stent thrombosis, termed late stent thrombosis (LST) [15]. LST is mainly associated with reduced re-endothelialisation of the stent, leading to a delayed healing of the vessel and over-exposure of the stent struts to the blood. Another possible reason for late thrombosis could be associated with adverse inflammatory responses to the drugs and the grafted polymer used in these stents. Extensive research has been undertaken to address the issues of in-stent restenosis and late-stent thrombosis, either through the development of more biocompatible polymer-based coatings [16,17] or by integrating specific antibodies with the ability to recruit and immobilize endothelial progenitor cells [18–20], thus promoting re-endothelialisation. The incorporation of nitric oxide (NO) donors in the stent design has also been considered as an encouraging alternative platform to reduce in-stent restenosis and LST. NO is an endogenous signalling molecule that participates in important biological processes and possesses several vasculoprotective properties [21]. It has been shown that the administration of different NO donors inhibits the proliferation and migration of SMC [22,23], enhances the proliferation of endothelial cells [24], prevents platelet aggregation [25] and adhesion [26] to the vascular endothelium and reduces intimal hyperplasia following vascular injury [27]. The delivery of NO through eluting stent platforms has been achieved by incorporating NO donors in a polyurethane polymer which was then coated onto the stents [28] or by incorporating the NO donor with paclitaxel [29] (an anti-proliferative agent extensively used in the prevention of restenosis). However, no significant improvements in preventing