Acta Biomaterialia 8 (2012) 549–558

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Synthesis of biomimetic segmented polyurethanes as antifouling biomaterials

I. Francolini *, F. Crisante, A. Martinelli, L. D'Ilario, A. Piozzi

Department of Chemistry, "Sapienza" University of Rome, Piazzale Aldo Moro, 5, 00185 Rome, Italy

ARTICLE INFO

Article history:
Received 24 June 2011
Received in revised form 22 September 2011
Accepted 17 October 2011
Available online 22 October 2011

Keywords:
Polyurethanes
Heparin-like polymers
Antifouling surfaces
Biomimetic polymers
Bacterial adhesion

ABSTRACT

Controlling the non-specific adsorption of proteins, cells and bacteria onto biomaterial surfaces is of crucial importance for the development of medical devices with specific levels of performance. Among the strategies pursued to control the interactions between material surfaces and biological tissues, the immobilization of non-fouling polymers on biomaterial surfaces as well as the synthesis of the so-called biomimetic polymers are considered promising approaches to elicit specific cellular responses. In this study, in order to obtain materials able to prevent infectious and thrombotic complications related to the use of blood-contacting medical devices, heparin-mimetic segmented polyurethanes were synthesized and fully characterized. Specifically, sulfate or sulfamate groups, known to be responsible for the biological activity of heparin, were introduced into the side chain of a carboxylated polyurethane. Due to the introduction of these groups, the obtained polymers possessed a higher hard/soft phase segregation (lower glass transition temperatures) and a greater hydrophilicity than the pristine polymer. In addition, the synthesized polymers were able to significantly delay the activated partial thromboplastin time, this increased hemocompatibility being related both to polymer hydrophilicity and to the presence of the $-SO_3H$ groups. This last feature was also responsible for the ability of these biomimetic polymers to prevent the adhesion of a strain of *Staphylococcus epidermidis*.

1. Introduction

Segmented polyurethanes are an important class of thermoplastic elastomers, being widely employed in the medical field for the manufacture of medical devices such as vascular grafts, catheters, artificial blood vessels and heart valves. Their successful employment in clinics is mainly related to their good blood compatibility and suitable mechanical properties arising from their structure of hard and soft segments [1].

One of the main drawbacks related with the use of blood-contacting medical devices is the high risk of infections and thrombosis associated with their implantation [2,3], these two complications being closely interrelated. In fact, upon exposure to the biological environment, plasma proteins, including fibrin, albumin and fibrinogen, adsorb on the device's surface, allowing the adhesion and activation of platelets and leukocytes. This process, known as biofouling, is usually the first stage of a cascade of biological events which leads to blood clot formation and promotes bacterial adhesion and biofilm formation on device surfaces. The resulting infectious and thrombotic complications can impair the function of the device and lead to implant failure and life-threatening consequences, as in the case of vascular grafts.

A common approach pursued to reduce biofouling is the immobilization of non-fouling polymers on biomaterial surfaces. This strategy is particularly interesting since it avoids the use of drugs (either by systemic administration or by local release from medicated devices) that, when administered over long periods of time, may be associated with undesired side effects.

On the basis of the empirical criteria recently proposed by Ostuni and colleagues [4], non-fouling polymers should be hydrophilic, electrically neutral and possess hydrogen-bond acceptors. Accordingly, several polymer classes have been explored [5], including polyacrylates [6], polyzwitterions [7,8] and poly(ethylene glycol) (PEG) derivates [9,10]. Of these, PEG, which has the ability to impart protein resistance, believed to be related to both hydration and steric effects [11], is the most widely studied non-fouling polymer. It has been grafted onto the surface of a series of materials, including glass [12], gold [13], poly(ethylene terephthalate) [14] and polyurethanes [15] with variable degrees of success, depending on the PEG's molecular weight, degree of branching and surface packing density. Although PEG possesses unique properties of non-toxicity and biocompatibility, a number of limitations have been associated with PEG grafting, including stability (autoxidation) and poor functionality [16]. Therefore, research in this field is still focused on the development of a more efficacious approach to obtain surfaces resistant to fouling by proteins, cells and bacteria.

In this regard, the synthesis of biomimetic polymers [17–20], i.e. materials able to mime the biological environment, has lately

* Corresponding author. Fax: +39 06 49913162.
E-mail address: iolanda.francolini@uniroma1.it (I. Francolini).

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doi:10.1016/j.actbio.2011.10.024