Biomaterials 71 (2015) 132–144

Contents lists available at ScienceDirect

Biomaterials

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

Antibiotic-loaded polypropylene surgical meshes with suitable biological behaviour by plasma functionalization and polymerization

C. Labay [a, b], J.M. Canal [a], M. Modic [c], U. Cvelbar [c], M. Quiles [d], M. Armengol [d], M.A. Arbos [d], F.J. Gil [b], C. Canal [b, *]

[a] Surfaces, Products and Textile Processes Research Group, Textile and Paper Engineering Dept., Technical University of Catalonia (UPC), C/ Colom, 1, 08222, Terrassa, Spain
[b] Biomaterials, Biomechanics and Tissue Engineering Group, Materials Science and Metallurgy Dept., UPC, Av. Diagonal 647, 08028, Barcelona, Spain
[c] Department F4, Jozef Stefan Institute, Jamova cesta 39, SI-1000, Ljubljana, Slovenia
[d] Grup de Recerca en Cirurgia General – VHIR, Universitat Autònoma de Barcelona, Passeig de la Vall d'Hebron, 119-129, 08035, Spain

ARTICLE INFO

Article history:
Received 27 March 2015
Received in revised form
4 August 2015
Accepted 14 August 2015
Available online 19 August 2015

Keywords:
Surgical mesh
Polypropylene
Plasma
Drug delivery
Surface modification
Fibroblast

ABSTRACT

Hernia repair is one of the most common operations in general surgery, and its associated complications typically relate to infections, among others. The loading of antibiotics to surgical meshes to deliver them locally in the abdominal hernia repair site can be one way to manage infections associated with surgical implants. However, the amount of drug loaded is restricted by the low wettability of polypropylene (PP). In this work, plasma has been used to tailor the surface properties of PP meshes to obtain high loading of ampicillin while conserving the desired biological properties of the unmodified samples and conferring them with antibacterial activity. It was demonstrated that the new surface chemistry and improved wettability led to 3-fold higher antibiotic loading. Subsequently, a PEG-like dry coating was deposited from tetraglyme with low-pressure plasma which allowed maintaining the high drug loading and kept cell properties such as chemotaxis, adhesion and morphology to the same levels as the untreated ones which have shown long-standing clinical success.

1. Introduction

In the past decade, polypropylene (PP) meshes have been used as prosthetic biomaterials not only to buttress the defect of incisional hernias, abdominal or inguinal, creating a tension-free repair [1–4] but also for the treatment of stress urinary incontinence [5], for vaginal prolapse [6] or to prevent prosthetic device infection [7]. Abdominal hernia is the protrusion of intra-abdominal content through the abdominal wall [1] from which around 1 million patients in the USA alone undergo repair surgery [8]. It has been shown that there are major physico-chemical differences between available meshes, which, in combination with the location of the mesh, the surgical technique applied and hernia type involved influence the infection potential [1]. Prosthetic device infection is a broad problem that can occur at varied stages of the materials lifespan and can be acute or delayed in their presentation [9]. The nature of device infections requires both preventive and therapeutic strategies. One of the current approaches to prevention includes the use of prophylactic preoperative systemic antibiotics. This approach should achieve adequate local tissue antimicrobial levels to fight the infection but comes at the risk of systemic effects secondary to the antibiotic exposure [7]. Several studies have shown the benefits of different kinds of antibiotics (such as cefazolin, ampicillin/sulbactam, amoxicillin or ampicillin/clavulanic acid) in the prevention of postoperative surgical site infection after inguinal PP mesh hernia repair [10–13]. However, as highlighted in the review by Bratzler et al. [10], randomized controlled trials have failed to identify an agent that is clearly superior to other agents for surgical site infection prophylaxis in hernia repair.

In recent developments, the focus has turned to improve surgical meshes incorporating cyclodextrin and maltodextrin for the prolonged release of ciprofloxacin from a PP artificial abdominal wall implant [14] or a degradable polycaprolactone/polylactide multilayer coating obtained by spraying onto PP as a carrier for the sustained release of ofloxacin and rifampicin [15]. However, PP has

* Corresponding author. Biomaterials, Biomechanics and Tissue Engineering Group, Materials Science and Metallurgy Dept., UPC, Av. Diagonal 647, 08028, Barcelona, Spain.
E-mail address: cristina.canal@upc.edu (C. Canal).

http://dx.doi.org/10.1016/j.biomaterials.2015.08.023
0142-9612/

low wettability and adhesion, impairing the loading of molecules directly in the polymer. Thus, Nistico et al. pre-treated PP meshes with atmospheric pressure plasma dielectric barrier discharge to enhance the surface adhesion of the biopolymer chitosan which has antibacterial properties itself [16].

Plasma treatment of polymer substrates has been commonly employed to tailor surface adhesion and wetting properties by changing the surface chemical composition [17–20]. Broadly, the plasma state can be considered as a gaseous mixture of a number of active species, including oppositely-charged particles that preserve electrical charge neutrality [21]. Appropriate selection of the plasma source enables the introduction of diverse functional groups on the target surface to improve wettability, biocompatibility or to allow subsequent covalent immobilization or physical adsorption of various molecules such as dyestuffs [22], pharmaceutical or cosmetic active principles [23,24]. Plasma can also be used for the deposition of thin polymer films by the so-called plasma polymerization process. Coating by plasma polymerization is defined as the formation of thin polymer coatings, on a surface such as a polymeric biomaterial, under the influence of plasma conditions [25,26]. By modifying the process parameters and the precursor molecule, different kinds of biocompatible coatings can be produced, from cell-adhesive coatings to anti-fouling coatings.

The aim of the present work is to obtain antibiotic-loaded PP meshes with enhanced drug loading on the materials while preserving their biological behaviour using a novel approach by combining different plasma processes. Thus, plasma surface functionalization of PP meshes is investigated to increase the potential amount of ampicillin loading. As the expected wettability enhancement produced by plasma may modify the biological behaviour of the material, low pressure plasma polymerization with a PEG-like precursor was examined to obtain a thin layer of polymer on the surface through a dry method. To understand better the processes, the physicochemical material properties were studied at different stages of treatment along with material performance of drug release, antibacterial activity and cell adhesion.

2. Experimental part

2.1. Materials

A polypropylene surgical knitted mesh, made from a 0.15 mm diameter monofilament, with 1.3 × 1.0 mm pore size and 97.0 ± 2.0 g/m^2 weight, (*SurgicalMesh*^{TM}, USA) was selected for this research. For contact angle measurements a PP film (*Goodfellow*) was used as a model surface. To avoid the potential influence of the additives used during polypropylene manufacture on the wetting properties of the materials, we prepared the surface of both materials by washing following the same protocol [24].

Ampicillin sodium salt (371.39 g/mol), provided by *Sigma Aldrich*® was selected for incorporation in the PP mesh, and presents a water solubility of 50 mg/mL.

Tetraethylene glycol dimethyl ether (tetraglyme, *Sigma Aldrich*) $CH_3O(CH_2CH_2O)_4CH_3$) was used as precursor for plasma polymerization. Phosphate buffer saline (PBS), pH 7.4, was prepared from KH_2PO_4 (*Fagron Iberica S.A.V*, Spain), Na_2HPO_4 (*Probus S.A*, Spain), NaCl (*Acofarma*®, Spain), and Milli-Q® deionized water. All chemicals used were of analytical grade. Orthophosphoric acid (H_3PO_4), 85% purity, from *Scharlab S.L.* (Spain) was used to adjust the pH value of the phosphate buffer solution.

Agar bacteriological (*Scharlau S.A.*, Spain) and Brain Heart Infusion Broth (BHI Broth) (*Scharlau S.A.*, 02–599, Spain) were used to prepare the bacteriological culture media of *Staphylococcus aureus* and *Escherichia coli*.

2.2. Plasma surface functionalization

Plasma functionalization treatments (F-) at atmospheric pressure were carried out by means of an *Ahlbrandt FG-2 (Germany)* corona plasma using air as the plasma forming gas. The distance between the electrode and the fabric was adjusted to 10 mm. During the treatments, power, speed and discharge current were kept constant at 380 W, 15 r.p.m. and 1.90 A respectively. Fabrics were treated for 1.05s, 1.75s, 3.5s and 7.0s (samples are coded as F-1.05s, F-1.75s, F-3.5s, F-7s) (Fig. 1).

To minimize the ageing process of all plasma-treated samples [27–29], analysis and post-treatments (including fabric loading) were carried out immediately following plasma treatment of the fabrics.

2.3. Plasma polymerization coatings

Plasma polymerization of polyethylene glycol (PEG) was carried out with low-pressure radio-frequency plasma (13.56 MHz) (Standard Femto Plasma System, *Diener*, Germany), by introducing tetraglyme in the plasma chamber by bubbling a carrier gas (argon) through liquid tetraglyme. Polymerization treatment was performed at 0.4 mbar for 2 h at an average power of 200 W; the plasma was pulsed with a pulse width of 20 μs with 20 ms between pulses. Before polymerization, a short surface activation step was carried out with argon, at 0.40 mbar of pressure for 30 s at 100 W.

2.4. Antibiotic loading of PP meshes

Polypropylene meshes were cut into rectangular samples of (7.0 × 5.0) cm, weighing approximately 0.32 g each. Loading of the PP samples was carried out by immersion in a 4% ampicillin solution in distilled water at a fabric/bath ratio of 1/10, during 24 h with continuous shaking at 160 r.p.m. at 20 °C. Subsequently, PP samples were submitted to a double padding process under 1 kg/cm^2 pneumatic pressure and 1 m/min speed working conditions. Samples were finally dried in an oven during 24 h at 37 °C. The samples were weighed before and after the loading process to calculate the amount of caffeine in the fibres and the loading ratio. A minimum of 4 replicates were done for each kind of sample.

2.5. In vitro release assays

Drug release assays were adapted from the USP dissolution test [30]. Five thermo-stabilized vessels were filled with 300 mL of PBS (pH 7.4), the stirring rate and temperature were maintained at 25 r.p.m. and 37 °C respectively, during the 4 h of the release experiment. The PP meshes were placed on a vertical stainless steel holder that ensures optimum contact between the textile materials and the buffer solution. 1 mL samples were withdrawn from the receptor compartment for latter spectroscopy analysis [23]. After each sample withdrawal, the same volume of fresh PBS was added to the receptor medium. Sink conditions were kept constant in the receptor solution during the experiment [31]. 4 replicates of antibiotic-loaded PP with the different treatments were studied, together with an un-loaded mesh used as a reference.

2.6. Surface topography analysis

Topography of the untreated and plasma treated PP meshes was studied by Field-Emission Scanning Electron Microscopy using a *Jeol JSM 5000 SEM*. All samples were Au coated prior to SEM observation. Observations were carried out at 15 kV working voltage.