Acta Biomaterialia 7 (2011) 2053–2059

Contents lists available at ScienceDirect

Acta Biomaterialia

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

Development of robust biocompatible silicone with high resistance to protein adsorption and bacterial adhesion

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ARTICLE INFO

Article history:
Received 9 August 2010
Received in revised form 27 January 2011
Accepted 2 February 2011
Available online 17 February 2011

Keywords:
Silicone
Hydrolysis
Non-fouling
Hydrophilic
Bacterial adhesion

ABSTRACT

A new biocompatible silicone comprising a carboxybetaine (CB) ester analogue, 3-methacryloxypropyltris-(trimethylsiloxy)silane (TRIS) and an organic silicone macromer (bis-α,ω-(methacryloxypropyl) polydimethylsiloxane) has been developed using photo-polymerisation. Following interfacial hydrolysis of the CB ester, the resulting zwitterionic material became significantly more hydrophilic and exhibited high resistance to both non-specific protein adsorption and bacterial adhesion. Moreover, the stability of these non-fouling properties was dramatically improved by using a slow and controlled rate of ester hydrolysis of the original protective hydrophobic matrix. The subsequent ability to maintain the original optical and mechanical properties of the bare silicone following surface activation makes this material an ideal candidate for preparing contact lenses and other medical devices.

1. Introduction

Silicone is frequently encountered in many biomedical applications, including cardiac pacemakers, intraocular lenses, syringes, ventricular shunts, antacids, artificial joints and implantable contraceptives. For example, breast implants usually consist of a silicone envelope that encases either saline or a combination of silicone oil and a gel [1]. The chemical inertness, lack of toxicity, high oxygen permeability and excellent optical properties of silicone make this biomaterial highly useful [2]. However, silicone-based materials have been shown to allow significant amounts of non-specific protein adsorption due to high levels of hydrophobicity [3], which results in poor biocompatibility in vivo. This phenomenon of protein fouling can be associated with several complications that occur during the use of silicone materials, including localised inflammation, infection and a variety of immunologically mediated diseases [4–7]. This can be illustrated by the use of implantable shunts for the treatment of hydrocephalus, which suffer primarily from obstruction (30%) and infection [8–10] leading to mortality and morbidity [11–13]. Thus, there is an urgent need to develop a robust silicone with non-fouling properties while maintaining its original desired characteristics.

To date, the enhancement of silicone to prevent non-specific protein adsorption has focused on the development of surface modification and co-polymerisation strategies using hydrophilic monomers. This has resulted primarily in the use of plasma treatment [14,15] or polymer grafting techniques (i.e. "graft to" and "grafted from") for the production of non-fouling surfaces [16–19]. A blood compatible silicone rubber membrane produced by plasma-induced grafted co-polymerisation of 2-methacryloyloxyethyl phosphorylcholine was developed Kao and co-workers [15]. Recently, an effective method of incorporating initiators for atom transfer radical polymerisation (ATRP) on polydimethylsiloxane (PDMS) was reported by Ma and co-workers [20]. This enabled polymers to be conveniently grown from a PDMS material (i.e. using a "grafted from approach"). Another strategy involves the incorporation of hydrophilic monomers such as polyethylene glycol methacrylate (PEGMA), vinyl pyrrolidone (NVP), *N*,*N*-dimethylacrylamide (DMA) and hydroxyethyl methacrylate (HEMA) [21] to obtaining protein resistance. Recently, Ishihara and co-workers developed a silicone hydrogel using zwitterionic phosphorylcholine (PC) groups to obtain non-fouling, extended wear contact lenses [22]. However, the use non-fouling/low fouling monomers with ATRP and hydrogels to modify silicone-based substrates results in significant hydration (necessary for protein resistance), which also allows other small molecules (e.g. H_2O_2) and ions (e.g. Fe^{3+}) to be present near the surface. This subjects the entire surface coating to harsh environments that allow both hydrolysis and oxidation to occur and is especially important to the base anchoring molecules of polymers and hydrogels. The degradation of these immobilizing linkers can lead to a total loss of the protecting non-fouling layer [23,24]. Thus, it is essential to develop a method to reduce exposure of the internal molecules of highly hydrated non-fouling materials to these harsh conditions and thereby prevent protein adsorption in long-term applications.

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doi:10.1016/j.actbio.2011.02.001

Upon close investigation of protein-resistant materials developed in recent years poly-zwitterionic materials such as poly-(2-methacryloyloxyethyl phosphorylcholine) (pMPC) [25–27], poly(sulfobetaine) (pSB) [28–30] and poly(carboxybetaine) (pCB) [31–33] have been shown to have excellent non-fouling and biocompatibility properties. This is due to their high levels of hydration (i.e. hydrophilicity), in addition to containing biomimetic-like structures which also make these zwitterionic materials excellent candidates for long-term application. Moreover, bifunctional zwitterionic coatings are also being developed (e.g. switchable polymer coatings with self-sterilizing and non-fouling/biocompatibility capabilities have been demonstrated [34]). This has opened the door to more advanced materials with specific functionalities. Lastly, while commonly used non-fouling polyethylene glycol (PEG) and its derivatives have been shown to degrade in the presence of oxygen and transition metal ions [35], zwitterionic materials have the potential to offer improved stability and thus surface coatings with more effective protein resistance.

In order to obtain a uniquely robust and biocompatible silicone with high resistance to non-specific protein adsorption and bacterial adhesion, we designed a hydrophobic CB ester analogue. The analogue consisted of an esterified carboxybetaine (i.e. the carboxylate anion converted to the corresponding ester) combined with a tertiary amine, which could be homogeneously mixed with hydrophobic 3-methacryloxypropyltris(trimethylsiloxy)silane (TRIS) without any additional solvent. The silicone was then prepared via photo-polymerisation of a reaction solution consisting of the CB ester analogue, TRIS and an organic silicone macromer (bis-α,ω-(methacryloxypropyl) polydimethylsiloxane). This resulted in the formation of a stable hydrophobic matrix capable of avoiding contact with "harsh" aqueous environments and thus provided protection for the CB ester analogues. Upon exposure to a hydrolysing environment only those esters near the outer surface of the hydrophobic matrix could be gradually converted into the protein-resistant zwitterionic form of CB. As the material slowly degrades inward, the eroded film can be replaced by newly hydrolysed analogues in the hydrophobic matrix, thereby maintaining the non-fouling properties over the period of application (Scheme 1). Here we report our investigation of this new biocompatible silicone.

2. Materials and methods

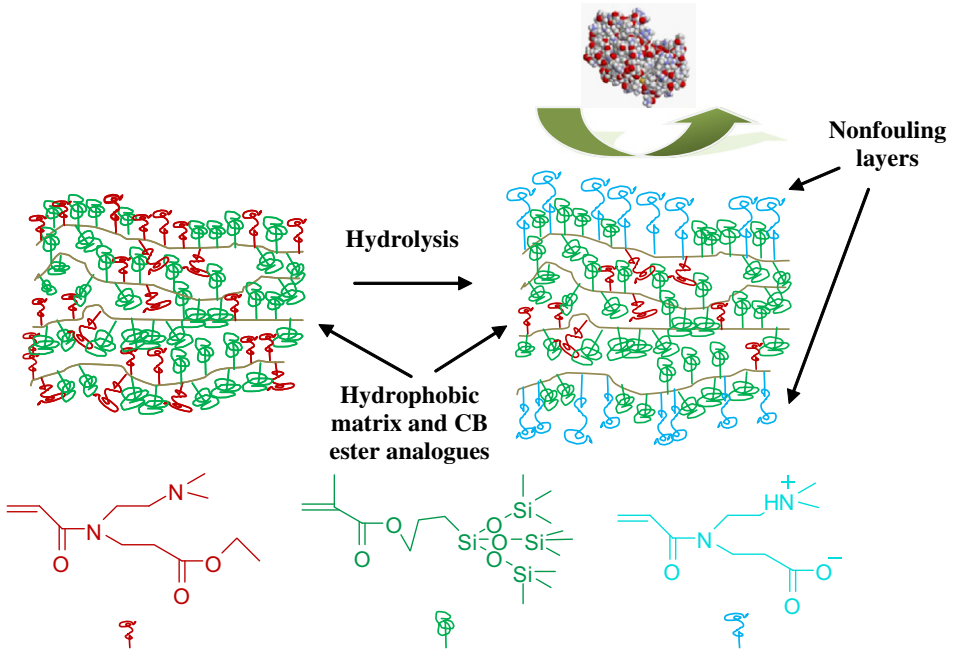
2.1. Materials

Horseradish peroxidase (HRP)-conjugated goat anti-human IgG(H + L) was purchased from Beijing Biosynthesis Biotechnology Co. *N,N*-dimethyl ethylene diamine (⩾98%), ethyl acrylate (⩾99%), acryloyl chloride (⩾96%), ethylene glycol dimethacrylate (EGDMA) (⩾98%) and 2,4,6-trimethylbenzoyl diphenyl phosphine oxide (Darocur® TPO, ⩾97%) were purchased from Aladdin Reagents (Shanghai). The macromer bis-α,ω-(methacryloxypropyl) polydimethylsiloxane (M_n 4000–6000, viscosity 50–100 cSt) and TRIS were purchased from Meryer Chemical. All other chemicals were of reagent grade. All chemicals were used without further purification.

2.2. Synthesis of carboxybetaine ester analogue

Ethyl acrylate was first added to *N,N*-dimethyl ethylene diamine at room temperature. The mixture was stirred for 1 h and distilled to provide compound 3 as a colourless oil (boiling point 108–111 °C at 5 torr). ^{1}H NMR (400 MHz, $CDCl_3$): 4.13 (q, 2H), 2.89 (t, 2H), 2.67 (t, 2H), 2.47 (t, 2H), 2.39 (t, 2H), 2.21 (s, 6H), 1.24 (t, 3H).

Compound 3 was mixed with triethylamine and then added to anhydrous tetrahydrofuran. After adding acryloyl chloride dropwise at 0 °C the reaction was allowed to proceed overnight at room temperature under a nitrogen atmosphere. The mixture was then filtered, concentrated in vacuo at 30 °C and purified by chromatography (silica gel, 10% methylene chloride/methanol) to yield compound 5. ^{1}H NMR (400 MHz, $CDCl_3$): 6.55 (m, 1H), 6.35 (m, 1H), 5.68 (m, 1H), 4.13 (q, 2H), 3.68 (t, 2H), 3.48 (t, 2H), 2.62 (t, 2H), 2.43 (t, 2H), 2.24 (s, 6H), 1.23 (t, 3H). The yield of compound 5 (Scheme 2) was ~60% with a purity of ~99% by ^{1}H NMR.



Scheme 1. High resistance to protein adsorption and bacterial adhesion is obtained through slow and controlled hydrolysis of CB ester analogues from a hydrophobic silicone matrix.

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