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Development of a new photocrosslinkable biodegradable bioadhesive

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Abstract

Adhesives provide a needle-free method of wound closure and do not require local anaesthetics. Polymeric adhesives have been used for about 3 decades for joining several tissues of the organism. Also, they can accomplish other tasks, such as haemostasis and the ability to seal air leakages and have the potential to serve as delivery systems.

PCL was modified with 2-isocyanatoethylmethacrylate to form a macromer that was crosslinked via UV irradiation using Irgacure 2959 by CIBA® as the photoinitiating agent. The characterization of the materials was accomplished by: attenuated total reflectance–Fourier transform infrared (ATR-FTIR), swelling capacity determination, evaluation of adhesive capacity (by reaction with aminated substrates) and determination of surface energy by contact angle measurement. Thermal characterization of the adhesive was performed by dynamical mechanical thermal analysis (DMTA) and thermogravimetric analysis (TGA). The morphology of PCL networks was observed using scanning electron microscopy (SEM) both after crosslinking process and following biodegradation in human plasma.

The haemocompatibility of the membranes was also evaluated by thrombosis and haemolysis tests.

Keywords: Polycaprolactone; Tissue adhesive; Photocrosslinking; Thermal characterization; Haemocompatibility

1. Introduction

Although suturing remains the most common method of closing wounds, topical skin adhesives are increasingly being used by health professionals to replace sutures, staples and adhesive strips in the fields of trauma, plastic and other surgeries, emergency medicine and paediatrics. They represent a fast and less traumatic closure method that includes less pain and for that reason does not require anaesthesia and also eliminate the problem of suture removal. Another advantage of bioadhesives is the fact that they usually allow obtaining excellent cosmetic results. Tissue adhesives also present the potential to serve as delivery systems and can be engineered for slow, localized release of medications, such as pain treatment drugs, antibiotics (Fujimoto et al., 1997) or chemotherapy treatment. They can be used as vehicles to growth factors (Zarge et al., 1997), and actual cell lines to assist on healing, namely, in poorly healing tissues like cartilage (Hoemann et al., 2005).

Surgical adhesives must obey some clinical requirements. They must hold the two sides of the tissue together, until it is no longer necessary, and then they should be degraded to biocompatible products (Lipatova, 1986). Also, an adhesive would ideally present the ability to cure in a moist environment.

The most used surgical glues nowadays are the fibrin based adhesives (Silver et al., 1995; Dunn and Goa, 1999) and cyanoacrylates (Leahey et al., 1993; King and Kinney, 1999). The fibrin based adhesives present several problems, e.g. immunogenicity and risk of blood transmission diseases such as HIV and BSE. On the other hand, cyanoacrylates have been reported to degrade in aqueous media to produce formaldehyde, which causes inflammation and has got carcinogenicity potential.

Other options are now coming into light, and among the synthetic materials, urethane-based adhesives have been considered to be quite promising for this application. However, although

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several studies have already been conducted by other authors (Lipatova, 1986; Sheikh et al., 2001) and also by us in trying to develop urethane pre-polymers to be applied as bioadhesives, these have proved that despite the good adhesion results, the curing time is too long to face surgical demands. UV curable adhesives offer major advantages compared to pre-polymers systems, such as fast-curing rate, control of the polymerization heat evolution and are ideal for application to weakened and diseased tissue (Benson, 2002).

Kao et al. (1997) have prepared ultraviolet (UV) irradiation curable bioadhesives based on *N*-vinylpyrrolidone. Although these adhesives presented suitable adhesive strength, the UV induced setting time was of approximately 3 min, which is a value that should be improved when surgical applications are concerned.

In this paper we wish to report the synthesis of urethanes based on polycaprolactone diol (PCL). PCL consists on semi-crystalline linear biodegradable aliphatic polyester. The biodegradability of this compound is based on the susceptibility of its aliphatic ester linkage to hydrolysis and its products of degradation are either metabolised by being included in the tricarboxylic acid cycle or eliminated by renal secretion (Kweon et al., 2003). This polymer has been used in several medical applications already approved by the US Food and Drug Administration (Bezwada et al., 1995; Darney et al., 1989). Nowadays, PCL is being applied not only in the development of drug delivery systems (Giavaresi et al., 2004), and resorbable sutures (Tomihata et al., 1998), but also as a material for tissue regeneration (Sarasam and Madihally, 2005).

In this work, PCL was modified with 2-isocyanatoethylmethacrylate to form a macromer that was easily crosslinked via UV irradiation. Irgacure 2959 by CIBA® was used as the photoinitiating agent since it was proved to be well tolerated over a wide range of cell types and chemical concentrations (Williams et al., 2005).

2. Experimental procedure

2.1. Materials

Hydroxyl end functionalized PCL diol (Mn ≈ 530), 2-isocyanatoethyl methacrylate (IEMA) and diethyl ether were purchased from Sigma/Aldrich Chemical Company (Spain) and used with no further treatment.

Human plasma was kindly supplied by the Coimbra University Hospital in the fresh frozen state in which was kept until use.

Rabbit venous blood used in haemocompatibility studies was colleted in polypropylene tubes with a 9:1 blood acid citrate dextrose (ACD) solution (ACD, 1995) ratio and was used immediately after collection.

2.2. Synthesis of the macromers

PCL macromers containing urethane groups were synthesized by modification of hydroxyl end functionalized PCL diol with IEMA. The ratio of NCO:OH groups used was 2:1 and the chosen solvent was diethyl ether because of its high volatility.

The reaction was performed by stirring the two components in a conventional two neck round-bottomed glass flask, in the absence of air (under a nitrogen atmosphere), and refluxing the solvent. The flask was placed in a water bath at the temperature of 40 °C. The ATR-FTIR technique showed that after 24 h of reaction all the NCO groups of the isocyanate had reacted with the PCL hydroxyl groups resulting in the formation of urethane groups. All these analysis were performed on a Magma-IR™ Spectrometer 750 from Nicolet Instrument Corp., equipped with a Golden Gate Single Reflection Diamond ATR. Spectra were recorded on an average of 128 scans at a resolution of 4 cm^{-1}.

2.3. Synthesis of the crosslinked networks by UV irradiation

The crosslinked networks were prepared by photocrosslinking with ultraviolet (UV) irradiation and using Irgacure 2959 by CIBA® as the photoinitiating agent.

The photoinitiator was added to the macromer solution in a percentage of 4% of the number of moles of the IEMA. The addition of the compound was done while the glass flask was still inside the water bath at 60 °C. The mixture was kept in reflux and in stirring conditions until complete solubilisation of Irgacure 2959. The resultant solution was removed from the water bath and was irradiated for the period of 60 s by using a UV lamp (*Model UVGL-48, Multiband UV*, from *Mineral light® Lamp*). After this period of time, a membrane was obtained.

2.4. Water sorption capacity

Three samples of crosslinked polymer were primarily dried until constant weight at 60 °C under vacuum conditions. The weight of the dried sample was obtained (W_d). These samples were then placed in a container with a saturated solution of pentahydrated copper sulphate and were weighted at different times until a maximum weight was achieved (W_s). The swelling ratio was evaluated by using Eq. (1).

$$\text{Swelling ratio}\,(\%) = \left(\frac{W_s - W_d}{W_d}\right) \times 100 \quad (1)$$

2.5. Evaluation of adhesive capacity – reaction with aminated substrate

In order to evaluate the binding capacity of the macromer, it was applied in the form of a solution containing the photoinitiator and placed between gelatine sheets that present a great amount of amino groups and therefore simulate the living tissues. The gelatine pieces dimension was of 1.5 × 3 cm and they were overlapped in 1 cm in which the adhesive was placed. The glued gelatine films had the final dimensions of 1.5 × 5 cm in total. They were then irradiated using the same conditions described for the synthesis of the crosslinked networks (60 s UV radiation). The macromer was therefore crosslinked between the aminated substrates.

The gelatine sheets were then subjected to the "pull to break" test, using a Chatillon TCD 1000 (Lloyd Instruments™,