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Modification of the biopolymer castor oil with free isocyanate groups to be applied as bioadhesive

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Abstract

Surgical adhesives have been used for several applications, including haemostasis, sealing air leakages and tissue adhesion. The aim of this work was to develop a biodegradable urethane-based bioadhesive containing free isocyanate groups. This material presents the advantage of being biodegradable, biocompatible and having the capacity of reacting with amino groups present in the biological molecules.

A urethane based on castor oil (CO) was synthesized by reaction of the molecule with isophorone diisocyanate (IPD). The characterization of the material was accomplished by different techniques: ATR–FT-IR (attenuated transmittance reflection–Fourier transform infrared), swelling capacity determination, evaluation of the moisture curing kinetics, reaction with aminated substrates and determination of surface energy by contact angle measurement. The study of the urethane thermal properties was performed by DMTA (dynamical mechanical thermal analysis) and TGA (thermogravimetric analysis). The haemocompatibility of the urethane was also evaluated by thrombosis and haemolysis tests.

Keywords: Surgical adhesives; Surface energy; Thermal analysis; Haemocompatibility

1. Introduction

Primary wound healing of a plan-to-plan oriented scar is usually accomplished by hand sewing or stapling the corresponding layers of each side of the incision [1]. Both these methods have been associated to wound infection. Suture strands can be classified according to their degradation properties as well as to their chemical composition. Natural absorbable suture strands are usually based on collagen and when implanted in living organisms are digested by body enzymes which attack and break down the strand. Synthetic absorbable sutures are based in synthetic polymers. When implanted they are hydrolyzed, resulting in the breakdown of the polymer chain. Hydrolyzation results in a lesser degree of tissue reaction than the enzymatic action suffered by natural absorbable sutures. Suture strands can also be nonabsorbable. These are not digested by body enzymes or hydrolyzed in body tissue and can be made from a variety of nonbiodegradable materials. The response of the organism to its presence involves a process of encapsulation by the body's fibroblasts. Nonabsorbable stands as well as metallic stapes have to be removed when applied in exterior skin closure.

To overcome these limitations surgeons have seeked alternative such as the use of medical tissue adhesives. These adhesives consist of an atractive alternative to suturing or stapling since they exhibit advantageous features, such as haemostasis sealing of air leakages and the elimination of the risk needle-stick injury to the surgeon. The use of an adhesive, being an easier and faster method to establish tissue adhesion, would also reduce the surgical procedure time. However, surgical adhesives must meet some clinical requirements. They must hold the two sides of the tissue together until it has enough mechanical strength to properly support wound healing and then they should be degraded to biocompatible products [2].

Nowadays, the most used surgical adhesives are based on fibrin [3,4] and cyanoacrylates [5,6]. The fibrin based adhesives present several problems, e.g. immunogenicity and risk of blood transmitted 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 have recently been explored and among the synthetic materials, urethane-based adhesives have been considered to be the most

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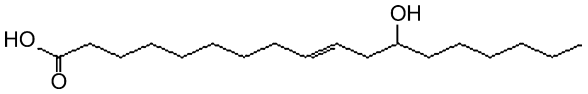

Fig. 1. Representation of the ricinoleic acid structure.

promising [7]. These materials are good candidates due to the possibility of being biodegradable, biocompatible and, if synthesised in the form of prepolymers, have the capacity to react with amino groups present in the biological molecules. This reaction results in the formation of urea linkages and also on the promotion of adhesion since these covalent bonds will hold the tissue together. An adhesive based on polyurethanes was synthesised and studied by Lipatova [8]. These authors showed that their degradation products did not present any toxic effect and that the glue was auto sterile and assured intensive haemostasis. Its potential as surgical adhesive was tested in several applications, such as renal surgery [9], endocrinology [10] and pancreatic occlusion [11]. Another advantage of the urethanes is the possibility of being biodegradable if they are synthesised from e.g. natural molecules, such as castor oil.

Castor oil is clear, almost colourless or pale yellow coloured viscous oil. This compound consists of a triglyceride of fatty acids, where, approximately, 90% of their content corresponds to the ricinoleic acid (Fig. 1).

This aliphatic carboxylic acid presents an 18-carbon chain, having a double bond between carbon 9 and 10 and a hydroxyl group on the carbon 12. This combination of hydroxyl group and unsaturation occurs exclusively in the castor oil molecule.

Although the plant from which the castor oil is extracted can be found through the world, it is mainly explored in Brazil and India. The composition of this natural oil is, however, extraordinarily well conserved independently of its origin (Fig. 2).

Castor oil is a vegetable oil that has found applications in many chemical industries [12]. When dehydrated, it is converted into a fast drying oil widely applied in paints, varnishes and even adhesives [13]. Its high water resistance makes it ideal for the use in all types of wrappings and packages for the food industry. This oil is also the primary raw material for the production of sebacic acid which is the basic ingredient for nylon production.

In the medical and pharmaceutical field, castor oil is mainly used in hospitals in colon RX patients' preparation since it presents laxative properties. This compound can also be found in several other products such as skin moisturisers (including lotions for solar burnings and dermatitis), cosmetics [14], creams or contraceptive gels, herbal preparations for labour stimulation [15], and systems of drug controlled release [16].

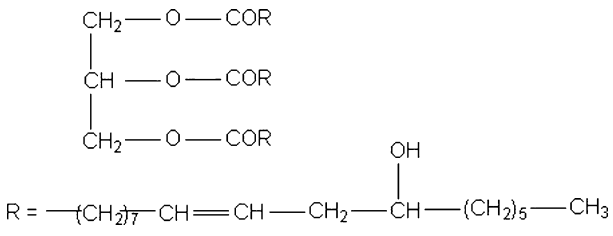

Fig. 2. Fundamental structure of castor oil.

The present paper describes the synthesis of a urethane based on castor oil in order to obtain a prepolymer with terminal isocyanate groups. The characterization of the urethane was accomplished by different techniques: ATR–FT-IR (attenuated total reflectance–Fourier transform infrared), swelling capacity determination, study of the stability of NCO groups under humidity conditions, reaction with aminated substrates and determination of surface energy by contact angle measurement. Thermal properties were also evaluated by DMTA and TGA. The haemocompatibility of the urethane was also evaluated by thrombosis and haemolysis tests.

2. Experimental procedure

2.1. Materials

All the reagents were purchased from Sigma/Aldrich Chemical Company (Spain) and used with no further treatment. Rabbit venous blood used in haemocompatibility studies was colleted in polypropylene tubes with a 9:1 blood ACD (acid citrate dextrose) solution [17] ratio and was used immediately after collection.

2.2. Synthesis

Urethanes based on castor oil were synthesized by modification of their hydroxyl groups with isophorone diisocyanate (IPD, Fig. 3). The ratio of NCO:OH groups used was 2:1.

The reactions were performed by stirring the two components at 60 °C under a nitrogen atmosphere. By ATR–FT-IR technique it was possible to observe that after 24 h of reaction, all the CO hydroxyl groups had reacted with the NCO groups of the isocyanate resulting in the formation of urethane groups. This technique was also employed to confirm the presence of free isocyanate groups in the prepolymer. All the ATR–FT-IR analysis were performed on a Magma-IR^{TM} 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. Swelling, moisture curing kinetics and reaction with aminated substrates

The moisture curing kinetics was determined by evaluating the stability of the NCO groups present in the prepolymers when

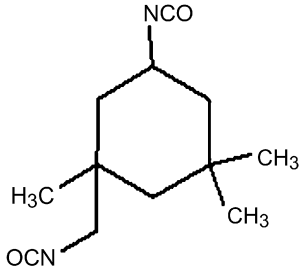

Fig. 3. Structure of isophorone diisocyanate (IPD) used to synthesize the urethanes.