

**BIOCOMPATIBLE BIORESORBABLE AND
NON-TOXIC ADHESIVE COMPOSITION
FOR SURGICAL USE**

The present invention is in the field of adhesive compositions which are intended for surgical use. The invention relates more precisely to a biocompatible, bioresorbable and non-toxic adhesive composition for the bonding, in particular, of biological tissues, including living tissues, to one another or for the bonding of biological tissues and an implanted biomaterial, which composition is based on non-crosslinked collagen or gelatin modified by oxidative cleavage and soluble in an acidic medium.

The invention also relates to the intermediate products which are used in the preparation of the above-mentioned adhesive compositions and to a process for their preparation and additionally relates to adhesive kits which are intended for extemporaneous surgical use.

The development and use of tissue glues for surgical use has been the subject of much research and numerous experimental studies for some decades.

One known adhesive composition, for example, consists of gelatin, resorcinol and formaldehyde (GRF) and was used between the 1960s and the 1980s. In this composite, the adhesive function is taken by the gelatin, polymerized by the formaldehyde, while the resorcinol (which is a phenol) is used to reduce the dissolution of the adhesive composition. Problems of tissue toxicity as well as of a lack of adhesion have been noted in a number of studies (Braunwald et al., *Surgery*, 59: 1024-1030 (1966); Bachet et al., *J. Thorac. Cardiovasc. Surg.*, 83: 212-217 (1982)). Moreover, it is no longer possible to consider employing formaldehyde in compositions for surgical use because of the risks posed by the release of this component and by its toxicity.

Also known is an adhesive system which was developed from a polypeptide isolated from the byssus of the mussel (marine adhesive protein) (Waite J. H. et al., *Biochem.*, 24: 5010-5014 (1985)). While originally extracted from the mussel, this protein was subsequently obtained by a synthetic route or by genetic manipulation (see in particular European Patent Application No. 242 656 and International Patent Application WO 88/03953, and Marumo et al., *Biochem. Biophys. Acts*, 872, 98-103 (1986); Swerdloff M. D. et al., *Int. J. Peptide Protein Res.*, 33, 313 (1989)). It is formed from a chain of repeating units which consist of a characteristic decapeptide rich in hydroxylatable tyrosine and proline residues and comprising DOPA (3,4-dihydroxyphenylalanine) which are responsible for these strong adhesion properties. Although promising at the conceptual level, this adhesive is nevertheless unavailable following difficulties in its development and because of the toxicity of certain forms of decapeptides. This system has been the subject of numerous patents (see in particular International Patent Application WO 92/10567 and the European patent applications published under Nos. 243 818 and 244 688; patents U.S. Pat. Nos. 4,808,702, 4,687,740 and AU-8 824 972).

However, it is in fact the development of a glue based on fibrinogen and thrombin which allowed the fields in which tissue glues are used to be truly developed.

The use of fibrinogen as a biomaterial for adhesive purposes dates from the beginning of the 1940s (Young, *Medawar, Lancet II*: 126-132 (1940)). After the initial results obtained in nerve anastomoses (Tarlov and Benjamin, *Surg. Gynecol. Obstet.*, 76 366-374 (1943)), this adhesive system was not satisfactory because of the low concentration of fibrinogen in the plasmas employed.

Then, in the 1970s, the idea of a glue was reintroduced by the use of a cryoprecipitate containing high concentrations of fibrinogen (Madras et al., *Wien Klin. Wochenschr.*, 87: 495-501 (1972)). This type of glue was subsequently commercialized by the company Immuno under the name "Tissucol" (Tisseel), then by Behringwerke under the name "Beriplast" and by Biotransfusion under the name "Bicol". The glue is a concentrated solution of fibrinogen (70-140 mg/ml) containing factor XIII and fibronectin, whose polymerization is induced by a solution of thrombin (4 to 400 International Units) in an extemporaneous mixture. The fibrinogen subsequently undergoes polymerization to form fibrin, forming a coagulum which brings about the adhesion of contacted tissues.

The major problems and difficulties raised by this product and its components are on the one hand the absence of complete characterization and reproducibility of the quantity of each of the components in the fibrinogen solution (factor XIII, fibronectin, aprotinin); and on the other hand the difficulty of absolute viral inactivation of such a product with regard to non-enveloped viruses such as unconventional transmissible agents. This has placed a limitation on the possibility of widespread use of such products in certain countries (for example the United States).

Finally, the European patent application published under the No. 0 466 383 (Bausch & Lomb Incorporated) has recently described an adhesive composition for surgical use consisting of crosslinked natural collagen, in which the fluidity and the concentration necessary on account of the intended surgical applications are regulated by the proportion of crosslinking in the collagen solution. According to this document, the desired fluidity and concentration are obtained by mixing a solution of highly crosslinked natural collagen and a solution of natural collagen having a lower degree of crosslinking. Biological tissues may be bonded applying the abovementioned mixture, heated beforehand so as to obtain a fluidity sufficient to enable its application to the tissues, then allowing it to cool.

However, this type of adhesive composition based on crosslinked collagen is difficult to handle and may give rise to problems with application because of the difficulties in making this composition sufficiently fluid. Indeed, the higher the proportion of crosslinked collagen, the greater the difficulty of reaching the degree of fluidity which is required for proper application to the biological tissues.

Moreover, the presence in this composition of collagen having a relatively low degree of crosslinking, although enhancing the fluidity of the mixture and thus the quality of application, places a limit on the mechanical strength.

It is in fact known that the mechanical strength and the biodegradability of collagen depend essentially on the degree of crosslinking and on the nature of the crosslinking brought about.

Moreover, European Patent Application No. 87 401 573.8 has disclosed a method of crosslinking collagen which makes it possible to crosslink the collagen in bulk and homogeneously without the covalent addition of a chemical molecule. Crosslinking is brought about by carrying out controlled oxidation of the collagen using a solution of periodic acid or sodium periodate at room temperature and in an acidic medium, then by continuing treatment at a basic or neutral pH. This method makes it possible to prepare insoluble, crosslinked collagen products (gels, films, powders, pellets or else bone filling products) which have good mechanical characteristics and good biodegradability, but is unsuitable for the preparation of fluid, liquid products.

The object of the invention is to provide a biocompatible, bioresorbable and non-toxic adhesive composition which is suitable for surgical use.