

## ADHESIVE COMPOSITION AND METHOD

This is a continuation of copending application(s) Ser. No. 07/908,474 filed on Jul. 6, 1992, now abandoned.

### BACKGROUND OF THE INVENTION

#### 1. Field of the Invention

This invention relates to adhesive compositions generally, and more particularly to tissue adhesives useful in the practice of medicine and surgery on human or animal subjects. In general, the adhesive is of high strength, stronger than sutures for example, and creates a non-toxic bond in 30 seconds or less. It works well under wet conditions.

The adhesive compositions are based on cross-linked proteinaceous material of human or animal origin. The compositions provide strong and rapid bonding to a wide range of substrates of natural or synthetic origin, providing a broad range of possible applications. Thus the compositions of present invention bond to living tissues, including muscle, skin, connective tissue, nerve tissue, vascular and cardiac tissues, adipose tissue, cartilage, bone, and the like, as well as to corresponding cadaver tissues, which may be preserved or otherwise chemically treated. Strong bonds are also formed to natural or synthetic materials such as leather, rubber, Dacron, Teflon, and the like, as well as to metals, enabling the use of these compositions for the attachment of surgical grafts and devices, as well as for wound closure, trauma repair, hemostasis, and the like in the practice of human or veterinary medicine. Non medical applications of the adhesive are also anticipated.

In addition to compositions, the invention further relates to the methods of generating the adhesive compositions, and to the methods of achieving bonding or hemostasis through the generation of these compositions in situ.

#### 2. Description of the Related Art

Various types of tissue adhesives are already known in the art. Three of these, namely the cyanoacrylates, gelatin-formaldehyde compositions, and fibrin based glues, have received most attention. For example, fibrin (a blood-clotting protein) and gelatin formaldehyde have each been utilized in surgical adhesive applications as have cyanoacrylates. Such adhesives work to a limited degree but have drawbacks as indicated below.

Several cyanoacrylates have been investigated for surgical use. For instance, some isobutyl cyanoacrylate formulations have been approved for veterinary use. Typically, monomer or a mixture of oligomers and/or monomer is applied to the site to be bonded where it rapidly polymerizes forming an adherent solid. One disadvantage of cyanoacrylate glues is that they require a dry field. Another is that the solid produced is non-absorbable, which limits the usefulness of the glue in internal applications. Also, the polymerization tends to be quite exothermic and adverse tissue response has been reported. There are a number of citations relating to this type of prior art indicated in the references listed at the end of this specification.

Glues based on gelatins cross linked with formaldehyde have been used experimentally, principally in Europe, since about 1964. Several formulations have been proposed of which "GRF" (gelatin, resorcinol, formol) is best known. Hot solutions of select gelatin are mixed in situ with a curing agent consisting primarily of formaldehyde solution. The mixture rapidly sets to a

solid which adheres to tissues. The chief objection to GRF glues has been the obligatory use of formaldehyde, a known hazardous material. Also, the gelatin must be applied hot, significantly above body temperature, and the techniques of mixing and application are quite critical for successful use of GRF. Pertinent references relating to GRF glues are listed in the References section.

Fibrin Glues utilize the natural processes of blood clot formation to generate an adhesive or sealant composition. One commercial product is "Tussicol"®, Rugis, France. Another is "Fibrin Sealant Kit 1.0" available from Osterreichisches Institut für Haemoderivate, GMBH, subsidiary of Immuno AG, A-1220, Vienna, Austria. Two components are combined to form an artificial blood clot. One of the components is a solution of fibrinogen and blood clotting factors such as Factor XIII, and the other is primarily a solution of thrombin and calcium ion. Disadvantages of fibrin glues include their very low strength (generally less than 50 g./sq. cm.) and relatively slow set up time. Also, the use of blood products (fibrinogen and co-factors) from multiple human donors presents an inherent risk of transmitting certain diseases to the patient. Procedures have been proposed for using autologous blood to prepare fibrin sealant. See for instance Reference 20 in the References section.

### SUMMARY OF THE INVENTION

As a surgical adhesive, the compositions of the invention have a bonding strength that is many times stronger than conventional fibrin adhesives and traditional sutures. For instance, several experimental surgical procedures were successfully carried out (in a porcine model) using the adhesive composition. For example, a perforated aorta and bowel were repaired by gluing patch materials to the lesions, and hemostasis was quickly achieved in a resected spleen by application of the adhesive.

The adhesive compositions of the present invention are the products of cross-linking on a surface or surfaces to be bonded of a mixture initially containing:

Part A.- a water soluble proteinaceous material of about 27-53% by weight of the mixture.

Part B.- di- or polyaldehydes present in a weight ratio of one part by weight to every 20-60 parts of protein present by weight in the mixture and water, optionally containing non essential ingredients to make up the balance of the composition. The final cross-linked bonding compositions are water insoluble, rubbery or leathery proteinaceous solids substantially free of aldehydes, and adherent to the substrate to be bonded with a tear strength of at least 75 g./sq. cm.

Bonding is achieved by combining the two part system (the parts being referred herein as Part A and B, respectively), and allowing the mixture to react on the surface or surfaces to be bonded. Bond formation is rapid, generally requiring less than one minute to complete. The resulting adhesion is strong, generally providing bonds with tear strengths of 400-600 g./sq.cm. Tear strengths of 1300 g./sq.cm. have been obtained by using this invention. The upper limits of tear strength have not been determined, and they are not intended to be interpreted as limiting the invention.

Part A is an aqueous solution containing about 30-55% by weight of purified or mixed protein material. The balance is water, dilute buffer, and/or saline