

ADHESIVE SEALANT COMPOSITION

The present invention is generally related to an adhesive sealant composition which may be used to bond or seal tissue in vivo and is particularly related to a two component, liquid adhesive composition which is mixed together as it is applied to tissue and then cured in vivo in order to bond tissue, to seal tissue to prevent or control pulmonary system air leaks, or to prevent tissue adhesions caused by surgery.

BACKGROUND

A variety of techniques have been used to bond or seal tissue. For example, different types of tissues have been mechanically bound or sealed with a number of procedures, materials and methods including sutures, staples, tapes and bandages. In some applications, these materials are made of absorbable materials which are intended to bond and/or seal tissue as it heals and then to be absorbed over a period of time.

The common use of a medical adhesive or "tissue glue" has not found widespread application. To date, some adhesive materials are known which may be used to adhere or stick tissue such as skin. For example, cyanoacrylate adhesives such as HISTOACRYL adhesive available from B. Braun, Melsungen, Germany or VETBOND tissue adhesive available from 3M, St. Paul, Minn. may be used to bond tissue. In addition to cyanoacrylate adhesives, other types of materials have been reported to adhere or stick to skin. For example, U.S. Pat. No. 4,839,345 to Doi et al. reports a hydrated crosslinked protein adhesive gel that is used as a cataplasm or cosmetic mask that will externally adhere to skin but can be easily removed or pulled off and then readhered to the skin. Other crosslinked protein hydrogels have been reported to serve as a proteinaceous substrate to deliver therapeutic agents such as enzymes or drugs through skin or mucous membranes. See, for example, International Patent Application Ser. No. PCT/US93/07314 filed Aug. 4, 1993. Still other materials have been used as hemostatic agents to stop or prevent bleeding. In particular, mixtures of fibrinogen and thrombin such as TISSEEL sealant available from Immuno AG, Vienna, Austria or BERIPLAST-P hemostatic agent or sealant available from Behringwerke, Marburg, Germany, have been used in vascular surgery to seal tissue such as blood vessels and thus prevent blood leakage.

In sum, there are few available adhesive compositions that have sufficient strength, biocompatibility and bioabsorbability as well as other desired properties that would allow such compositions to be readily used in current medical procedures or practices. The unavailability of a suitable tissue adhesive or sealant may be related to the stringent requirements that a suitable, useful tissue adhesive must meet. Importantly, a tissue adhesive must provide substantial bonding strength for either internal or external tissues. The adhesive should be made of a biocompatible material which does not interfere with normal healing or regeneration processes. A suitable tissue adhesive must also be easily administered in a liquid form and then rapidly cured, ideally in less than a minute, once applied. In addition, a tissue adhesive must remain flexible, pliant and have good mechanical strength after being cured. Finally, a tissue adhesive must be completely absorbed or broken down in vivo, without producing an allergic response, adverse tissue reaction or systemic toxic effects, in an acceptable time period. Preferably a suitable adhesive would also be readily absorbed after it is applied.

SUMMARY OF THE INVENTION

The present invention is a nontoxic, absorbable adhesive sealant composition which may be used to bond and/or seal tissue. The adhesive composition is readily formed from a two component mixture which includes a first part of a protein, preferably a serum protein such as albumin, in an aqueous buffer having a pH in the range of about 8.0-11.0 and a second part of a water-compatible or water-soluble bifunctional crosslinking agent. When the two parts of the mixture are combined, the mixture is initially liquid. The combined mixture then cures in vivo on the surface of tissue in less than about one minute to give a strong, flexible, pliant substantive composition which securely bonds to the tissue and is readily absorbed in about four to sixty days, preferably in about four to twenty-eight days.

In a preferred embodiment of the invention, an adhesive sealant composition is formed from a two part mixture that includes a proportion of a volume of a buffered basic serum albumin protein solution to a volume of a polyethylene glycol disuccinimidoyl succinate crosslinking agent in a range of from about 1:10 parts albumin solution by volume to about 10:1 parts by volume crosslinking agent. In order to facilitate the mixing of the two parts of the present adhesive composition, the volume to volume ratio of albumin solution to crosslinking agent is preferably a ratio of 1:1.

Preferred serum albumin proteins are selected to prevent adverse tissue or unwanted immunological responses. When the present adhesive mixture is used to bond or seal human tissue, a preferred serum albumin is purified human serum albumin which has been sterilized, dialyzed with a basic buffer having a pH value of about 8.0-11.0, concentrated by ultrafiltration through a membrane having about a 50,000 molecular weight cut-off to yield a concentrated, buffered aqueous mixture having about 20-60 wt/vol %, preferably about 35-45 wt/vol %, human serum albumin.

Preferred bifunctional crosslinking agents include polyethylene glycol derived crosslinking agents having a molecular weight (weight average) in a range of about 1,000-15,000 and preferably in a range of about 2,006-4,000. When the molecular weight of the crosslinking agent is in the range of about 1,000-5,000 the crosslinking agent is generally dissolved in water at a concentration of about 50-300 mg/ml. Similarly, when the molecular weight of the crosslinking agent is in the range of about 5,000-15,000 the crosslinking agent is generally dissolved in water at a concentration in the range of about 300-800 mg/ml.

The adhesive composition of this invention may be used in a variety of applications. Some applications include using the adhesive sealant composition to bind tissue together either as an adjunct to or as a replacement of sutures, staples, tapes and/or bandages. In another application, the present adhesive may be used to prevent post-surgical adhesions. In this application, the adhesive composition is applied and cured as a layer on surfaces of internal organs or tissues in order to prevent the formation of adhesions at a surgical site as the site heals. Additional applications include sealing tissues to prevent or control blood or other fluid leaks at suture or staple lines as well as to prevent or control air leaks in the pulmonary system.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graphical representation of a measured peel force of an adhesive composition of this invention.

FIG. 2 is a graphical representation of peel force measurements of different adhesive composition samples which are used to adhere excised guinea pig skin strips together.