

HEMOSTATIC TISSUE SEALANTS

CROSS REFERENCE TO RELATED APPLICATION

Priority is claimed to U.S. provisional application Ser. No. 60/054,849, filed on Aug. 6, 1997.

FIELD OF THE INVENTION

The present invention is in the field of tissue sealants, particularly tissue sealants with hemostatic activity.

BACKGROUND OF THE INVENTION

Tissue sealants are used to decrease or prevent the migration of fluid from or into a tissue. A well known material that has been used as a tissue sealant is "fibrin glue", which is typically made by contacting a solution or suspension of the blood protein fibrinogen with an enzyme or other reagent which will cause fibrin to crosslink. Typically, the enzyme thrombin is used, which cleaves the fibrinogen molecule at specific points to form fibrin monomer, which then spontaneously crosslinks. This is a natural reaction involved in the formation of blood clots. A familiar example of a crosslinked fibrin based material is a scab or an eschar. A disadvantage of fibrin glues is that they have little flexibility or extensibility once their deposition is complete. Moreover, fibrin can be biodegraded in a variable amount of time, depending on a number of uncontrolled parameters, and the duration of a fibrin based tissue sealant is not predictable. Adherence of fibrin clots to tissues can also be unpredictable.

As disclosed in PCT/US96/03834, synthetic materials can be used to make tissue sealants that exhibit high levels of tissue adherence, elastic compliance, and controlled biodegradability. Moreover, these synthetic sealants are completely free of viral and other biological hazards. However, synthetic sealants may not possess significant intrinsic hemostatic properties. Such properties are herein provided by the incorporation of hemostatic materials into one or more of the components of the sealant composition, in advance of or in concurrently with their application to tissue.

SUMMARY OF THE INVENTION

A method of controlling hemostasis by applying a hemostatic agent in a tissue sealant composition is described. The tissue sealant is a biodegradable, biocompatible synthetic polymer that may not intrinsically possess strong hemostatic properties. Inclusion of a hemostatic material in the tissue sealant can control bleeding at the site and may also provide improved adherence of the sealant to tissue and provide shorter healing times.

In a preferred embodiment the tissue sealant is a hydrogel formed from crosslinkable materials having hydrophilic portions and including crosslinkable groups. The hemostatic agent can be incorporated into the crosslinkable material which is applied to the area of tissue where it is desired that hemostasis be prevented. The crosslinkable material is then formed into a hydrogel that seals the tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph that illustrates the effect of dilution of rabbit blood on the time required for the blood to clot. The upper curve represents dilution with a gel forming macromer and the lower curve represents dilution with a saline control.

FIG. 2 is a bar graph that illustrates the effects of addition of various agents on the clotting time of blood diluted with saline and blood diluted with a gel forming agent.

DETAILED DESCRIPTION OF THE INVENTION

The materials described herein include crosslinkable molecules suitable for forming a tissue sealant, further incorporating hemostatic materials, also referred to hereinafter as "hemostats". A wide variety of hemostats may be of use, provided that they do not interfere with the formation of crosslinked materials, and are themselves still able to act after exposure to crosslinkable materials. The crosslinked sealant material is biocompatible, biodegradable, and has the ability to seal a tissue or organ against the leakage of bodily fluids, including air.

The crosslinked material is a hydrogel that adheres to tissue in the preferred embodiments. In one preferred embodiment, the hemostat is used in conjunction with a sealant that is applied to a tissue primed with an initiator. The compositions may contain other agents, including additional biologically active materials.

Definitions

A "sealant" is a material which decreases or prevents the migration of fluid from or into a tissue. Sealants are typically applied to a tissue and then locally crosslinked or otherwise processed. The same materials may also be used to adhere structures or tissues together, either when applied between them and crosslinked or processed, or when used to encase junctions of tissue and/or devices.

"Crosslink" is used generically to refer to the joining of smaller entities to form a structure by any physical or chemical means. Unless stated otherwise, the terms "polymerize" and "gel" are functional equivalents of "crosslink".

"Biocompatibility", in the context of the materials and devices of the invention, is the absence of stimulation of a severe, long-lived or escalating biological response to an implant or coating, and is distinguished from a mild inflammation which typically accompanies surgery or implantation of foreign objects into a living organism.

"Biodegradability", in the context of the materials and devices of the invention, is the predictable disintegration of an implant into entities which will be metabolized or excreted, under the conditions normally present in a mammalian organism or living tissue.

"Hemostat" or "hemostatic" refers to a material having the property of stopping the flow of blood, which may include stopping the flow of plasma. A hemostat or hemostatic material may work by any of several mechanisms, as further described.

"Water-soluble" refers to a material soluble to at least 1% by weight in water or an aqueous solution.

Polymeric Compositions

The hemostatic sealants are formed of a crosslinked material, preferably a hydrogel, into which a hemostatic agent is incorporated. The hydrogel is formed of crosslinkable materials (monomers) which contain crosslinkable groups, hydrophilic polymer regions, and preferably, biodegradable regions or linkages. The hydrogels can be formed (crosslinked) prior to application to the tissue or after application to the tissue.

In a preferred embodiment, the hydrogel is formed from biodegradable, polymerizable, macromolecular monomers (macromers) that include a core, an extension on each end of the core, and an end cap on each extension. The core is the hydrophilic polymer or oligomer; each extension is a biodegradable oligomer; and each end cap is an oligomer, dimer or monomer capable of crosslinking the macromers. In a particularly preferred embodiment, the core includes hydrophilic poly(ethylene glycol) oligomers of molecular weight between about 400 and 30,000 Da; each extension