VISCOELASTIC COLLAGEN SOLUTION FOR OPTHALMIC USE AND METHOD OF PREPARATION

This is a continuation-in-part of application Ser. No. 890,847 filed Aug. 6, 1986 and now U.S. Pat. No. 4,713,446 which is a continuation-in-part application of Ser. No. 773,310 filed Sept. 6, 1985 now abandoned.

FIELD OF THE INVENTION

This invention relates to a chemically-modified collagen compound which when dissolved in a physiological buffer has therapeutic application in a variety of medical applications, particularly in ophthalmic surgery. Specifically, the collagen solutions of this invention are useful in the following procedures: (a) as an anterior segment implant to maintain anterior chamber depth and to protect the corneal endothelium during intracapsular and extracapsular cataract lens extraction and during intraocular lens implantation; (b) as a surgical adjunct during corneal transplant surgery to protect the corneal endothelium from contacting other ocular tissue and to prevent post-operative graft dislocation; (c) as a posterior segment implant during intraocular lens implantation and as an adjunct to retinal detachment surgery; and (d) as a vitreous replacement. This invention also relates to the production of the collagen compound by reacting purified, native, pepsin-treated collagen with an amine-reactive coupling agent and a monofunctional amine-reactive modifying agent, either sequentially or simultaneously, and in a controlled manner so as to limit the degree of coupling.

BACKGROUND OF THE INVENTION

Sodium hyaluronate, collagen gels and chondroitin sulfate solutions have been used in the anterior chamber to protect the corneal endothelium from intraocular lens trauma and to maintain anterior chamber depth. Additionally, hyaluronate and collagen gels have been used as vitreous replacements. None of these materials has proven to be ideal in such applications.

Chondroitin sulfate solutions do not exhibit pseudoplastic behavior, i.e., the viscosity is relatively constant at all shear rates. Accordingly, chondroitin sulfate solutions do not exhibit the same degree of anterior chamber support as pseudoplastic fluids such as those prepared using sodium hyaluronate. Furthermore, since the viscosity of the chondroitin sulfate solutions does not decrease at increasing shear rates (as do pseudoplastic materials) extremely high pressures are needed to apply or irrigate chondroitin sulfate solutions through a syringe (MacRae et al., "The Effects of Sodium Hyaluronate, Chondroitin Sulfate, and Methyl Cellulose on the Corneal Endothelium and Intraocular Pressure," *American Journal of Ophthalmology,* 95:332–341 (1983)). Additionally, commercially available chondroitin sulfate solutions (20 to 50 percent solutions) have osmolarities in excess of 500 mOs_m. Such high osmolarities are detrimental to the corneal endothelium. Lastly, as reported by MacRae et al. in the American Journal of Ophthalmology, supra, 20 percent chondroitin sulfate may cause a sharp increase in intraocular pressure in the first one to four hours after intracameral injection and, therefore, anterior chamber washout is indicated.

Stenzel et al. ("Collagen Gels: Design for a Vitreous Replacement", *Science* 164: 1282–1283 (1969)), Dunn et al. ("Collagen-Derived Membrane: Corneal Implantation", *Science,* 157: 1329–1330 (1967)) and Rubin et al. ("Collagen as a Vehicle for Drug Delivery", *J. Clinical Pharmacology,* Aug-Sept., Pages 309–312 (1973)) have described the use of stabilized collagen membranes and gels to serve as drug delivery devices, vitreous replacement gels and cornea transplants. Introduction of crosslinks was accomplished by heat, ultraviolet radiation or glutaraldehyde reaction.

U.S. Pat. No. 4,409,332 discloses membranes and gels composed of complexes of reconstituted collagen with alkaline phosphatase, crosslinked with glutaraldehyde, UV radiation or gamma radiation. These complexes are said to be useful as vitreous replacements for ophthalmologic therapy.

U.S. Pat. No. 4,164,559 describes a chemically-modified collagen membrane which is useful as a carrier for ophthalmic medication. The collagen compounds disclosed are single collagen units which have been acylated or esterified.

Collagen as an anterior chamber replacement is described by Kawakami ("Operation for Aftercataract with the Injection of Collagen Gel into the Anterior Chamber", *Excerpta Medica International Congress Series,* Vol. 2 (450), pages 1432–1434 (1975)). This investigation describes the injection of ultraviolet crosslinked collagen gel into the anterior chamber prior to extraction of the aftercataract.

The collagen gels described hereinabove have greater viscosities and thus afford more protection and support to eye tissues than does chondroitin sulfate. However, known collagen gels are not pseudoplastic and fragment into small pieces when injected through a syringe. Additionally, collagen gels are generally hazy materials and have been known to cause inflammatory reactions in the anterior chamber and the vitreous (Advances in Vitreous Surgery, pages 601–623, Irvine and O'Malley, 1976).

Furthermore, collagen gels injected into the anterior chamber may cause an elevation of intraocular pressure (Kawakami, E., "Operation for Aftercataract with the Injection of Collagen Gel into the Anterior Chamber", supra).

Neither the chondroitin sulfate solutions nor the collagen gels used in ophthalmic surgery are viscoelastic materials. Viscoelastic ophthalmic materials are preferred for several reasons. During surgery, viscoelastic materials protect cell and tissue surfaces from mechanical trauma; create space by separating two adjacent but not adherent tissue surfaces, or by breaking normal or pathological tissue adhesions; maintain space allowing for safe surgical manipulations or by permitting the insertion of implants without dislocating or touching sensitive tissues; contain hemorrhages; and also act as a "soft instrument" or "surgical tool" to move, manipulate or relocate tissues.

After surgery, viscosurgical materials may be used to retain space for a desired period of time, prevent or minimize postsurgical inflammation and localize bleeding, restrain fibrin coagulation, hold back inflammatory cells, and lubricate tissue surfaces which move relative to each other and thereby prevent adhesion formation.

U.S. Pat. No. 4,141,973 discloses the use of highly-pure hyaluronic acid for both vitreous and aqueous replacement. This material is colorless, transparent, nontoxic and viscoelastic. However, it too has a number of drawbacks. The most abundant natural source of hyaluronic acid is rooster combs. Due to the low yield from this source coupled with the relatively compli-