

METHOD FOR BONDING SOFT TISSUE WITH COLLAGEN-BASED ADHESIVES AND SEALANTS

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FIELD AND BACKGROUND OF THE INVENTION

The ability to establish bonding between biological 10
tissues has long been a goal of biomedical researchers. Attempts to provide desired adhesion through mechanical bonding have proven to be neither convenient nor permanent (Buonocore, M., *Adhesion in Biological Systems*, R. S. Manly, ed., Academic Press, New York, 15
1970, Chap. 15). For this reason, much attention was devoted to developing synthetic polymers, e.g., cyanoacrylates, as biomedical adhesives. These plastic materials, however, have been observed to induce inflammatory tissue reaction. Moreover, the ability of these materials to establish permanent bonding under physiological conditions has yet to be fully realized.

The known toxicity associated with synthetic adhesives has led to investigations towards the development of biologically derived adhesives as bonding materials. 25
Among such adhesives, fibrin based glues have commanded considerable attention. (See, e.g., Epstein, G. H. et al. *Ann. Otol. Rhinol. Laryngol.* 95:40-45 (1986); Kram, H. B. et al. *Arch. Surg.* 119: 1398-1311 (1984); Scheele, J. et al. *Surgery* 95:6-12 (January 1984); and Siedentop, K. H. et al. *Laryngoscope* 93: 1310-1313 (1983) for general discussion of fibrin adhesives). Commercial fibrin tissue adhesives are derived from human plasma and hence pose potential health risks such as adverse immunogenic reactions and transmission of 30
infectious agents, e.g., Hepatitis B virus. Moreover, the bond strength imparted by such adhesives are relatively weak compared to collagen adhesives (see De Toledo, A. R. et al. *Asso. for Res. in Vision and Ophthalmology*, Annual Meeting Abstract, Vol. 31, 317 (1990). Accord- 40
ingly, there is a need for safe, effective biologically compatible tissue adhesives for biomedical applications.

Collagen, the major connective tissue protein in animals, possesses numerous characteristics not seen in synthetic polymers. Characteristics of collagen often 45
cited include good compatibility with living tissue, promotion of cell growth, and absorption and assimilation of implantations (Shimizu, R. et al. *Biomat. Med. Dev. Art. Org.*, 5(1): 49-66 (1977)). Various applications of this material are being tested, for example, as dialysis 50
membranes of artificial kidney (Sterzel, K. H. et al. *Amer. Soc. Artif. Int. Organs* 17: 293 (1971)), artificial cornea (Rubin, A. L. et al. *Nature* 230: 120 (1971) and U.S. Pat. No. 4,581,030), vitreous body (Dunn, M. et al. *Amer. Soc. Artif. Int. Organs* 17:421 (1971)), artificial 55
skin and blood vessels (Krajicek, M. et al. *J. Surg. Res.* 4, 290 (1964)), as hemostatic agents (U.S. Pat. No. 4,215,200), soft contact lens (U.S. Pat. Nos. 4,264,155; 4,264,493; 4,349,470; 4,388,428; 4,452,925 and 4,650,616) and in surgery (Chvapil, M. et al. *Int. Rev. Conn. Tiss.* 60
Res. 6: 1-61 (1973)). Natural collagen fibers, however, are basically insoluble in mature tissues because of covalent intermolecular crosslinks that convert collagen into an infinite crosslinked network. Dispersal and solubilization of native collagen can be achieved by treatment 65
with various proteolytic enzymes which disrupt the intermolecular bonds and removes immunogenic non-helical end regions without affecting the basic, rigid

triple-helical structure which imparts the desired characteristics of collagen (see U.S. Pat. Nos. 3,934,852; 3,121,049; 3,131,130; 3,314,861; 3,530,037; 3,949,073; 4,233,360 and 4,488,911 for general methods for preparing purified soluble collagen). Subsequent purification of the solubilized collagen can be accomplished by repeated precipitation at high pH or ionic strength, washing and resolubilization. Introduction of covalent crosslinks into the purified soluble collagen is an important aspect in stabilizing and restructuring the material for biomedical use.

Various methods and materials have been proposed for modifying collagen to render it more suitable as biomedical adhesives. (See, e.g., De Toledo, A. R. et al. *Asso. for Res. in Vision and Ophthalmology*, Annual Meeting Abstract, Vol. 31, 317 (1990); Lloyd et al., "Covalent Bonding of Collagen and Acrylic Polymers," *American Chemical Society Symposium on Biomedical and Dental Applications of Polymers*, Polymer Science and Technology, Vol. 14, Plenum Press (Gebelein and Koblitz eds.), New York, 1980, pp. 59-84; Shimizu et al., *Biomat. Med. Dev. Art. Org.*, 5(1): 49-66 (1977); and Shimizu et al., *Biomat. Med. Dev. Art. Org.*, 6(4): 375-391 (1978), for general discussion on collagen 25
and synthetic polymers.) In many instances, the prior modified collagen-based adhesives suffer from various deficiencies which include (1) crosslinking/polymerization reactions that generate exothermic heat, (2) long reaction times, and (3) reactions that are inoperative in the presence of oxygen and physiological pH ranges (Lee M. L. et al. *Adhesion in Biological Systems*, R. S. Manly, ed., Academic Press, New York, 1970, Chap. 17). Moreover, many of the prior modified collagen-based adhesives contain toxic materials, hence rendering it unsuitable for biomedical use (see, for example, Buonocore, M. G. (1970) and U.S. Pat. No. 3,453,222).

To date, there are no safe, efficacious adhesives for medical use with soft tissue. Collagen-based adhesives with appropriate adhesive strength would have enormous utility in many medical applications, particularly involving soft tissues. Such adhesives could be used to seal incisions following cataract removal and to attach epikeratophakic grafts to corneal tissue, etc. Marketing research has indicated that there are over 8 million surgical procedures that could use a safe, effective biological adhesive.

SUMMARY OF THE INVENTION

The present inventors have discovered that a biologically compatible, collagenous reaction product with sealant and adhesive properties can be formed using chemically modified collagen. Modification of pure, soluble or partially fibrillar collagen monomers with an acylating agent or a sulfonating agent or a combination of the foregoing, renders collagen monomers soluble at physiological conditions. Subsequent polymerization of the chemically modified monomers produces a polymerized collagen composition with adhesive and sealant properties. The polymerization reaction may be initiated with an appropriate polymerization initiator such as a chemical oxidant, ultraviolet irradiation, a suitable oxidative enzyme or atmospheric oxygen.

Accordingly, it is an object of the present invention to provide polymerized chemically modified collagen compositions as a safe, effective biological adhesives with appropriate adhesive strength for biomedical applications, particularly involving soft tissues. Such adhesives may be used to seal incisions following cataract