

**RAPID-GELLING BIOCOMPATIBLE  
POLYMER COMPOSITION AND  
ASSOCIATED METHODS OF PREPARATION  
AND USE**

**CROSS-REFERENCE TO RELATED  
APPLICATIONS**

This application is a continuation-in-part of U.S. application Ser. No. 09/293,708, filed Apr. 16, 1999, and now U.S. Pat. No. 6,312,725 the disclosure of which is incorporated herein by reference.

**TECHNICAL FIELD**

This invention relates generally to biocompatible polymer compositions that rapidly crosslink to form a gel. More particularly, the invention relates to a composition prepared by admixture of individually reactive polymer components, wherein the admixture initiates rapid crosslinking and gel formation. Such compositions are particularly well suited for use in a variety of tissue-related applications in which rapid adhesion to the tissue and gel formation is desired. Accordingly, the invention additionally relates to methods of using the compositions as bioadhesives, for tissue augmentation, in the prevention of surgical adhesions, for coating surfaces of synthetic implants, as drug delivery matrices, for ophthalmic applications, and in other applications, as discussed herein and/or as appreciated by one of ordinary skill in the art.

**BACKGROUND OF THE INVENTION**

The use of polymer compositions in tissue engineering is now widely recognized, particularly those compositions manufactured with synthetic polymers. In contrast to many naturally derived compositions, synthetic polymer compositions can be formulated to exhibit predetermined physical characteristics, such as gel strength, as well as biological characteristics, such as biodegradability.

In a variety of tissue engineering applications, it is desirable to use compositions that can be administered as liquids, but which subsequently form gels at the site of administration. Such in situ gel-forming compositions are convenient to use since they can be administered as liquids from a variety of different devices, and are adaptable for administration to any site, since they are not preformed. Many different mechanisms have been described that can be used to promote gel formation in situ. For example, photoactivatable mixtures of water-soluble co-polyester prepolymers and polyethylene glycol have been described as useful in the preparation of gel barriers and drug release matrices. In another approach, block copolymers of a Pluronic™ poloxamer have been designed that are soluble in cold water, but form insoluble gels that adhere to tissues at body temperature (Leach et al. (1990) *Am. J. Obstet. Gynecol.* 162: 1317-1319 (1990)). Polymerizable cyanoacrylates have also been described for use as tissue adhesives (Ellis, et al. (1990) *J. Otolaryngol.* 19:68-72 (1990)). In yet another approach, two-part synthetic polymer compositions have been described that, when mixed together, form covalent bonds with one another, as well as with exposed tissue surfaces. (PCT WO 97/22371, which corresponds to U.S. application Ser. No. 08/769,806.) In a similar approach involving a two-part composition, a mixture of a protein and a bifunctional crosslinking agent has been described for use as a tissue adhesive (U.S. Pat. No. 5,583,114.) One difficulty encountered when designing in situ gel forming compositions is that optimizing the composition to enhance gel

formation may worsen tissue inflammation at the site of administration. A possible explanation for this effect is that highly reactive composition components that are capable of rapid gel formation may adversely affect tissue surfaces.

The compositions of the present invention have been formulated to provide for rapid gelation, while decreasing the likelihood and/or severity of tissue inflammation at the site of administration relative to that associated with the previously described compositions.

**SUMMARY OF THE INVENTION**

Accordingly, in one aspect of the invention, a reactive polymer composition is provided that comprises an admixture of two or more biocompatible, reactive components selected so as to rapidly react with each other to form a crosslinked gel. The first component, component "A," is a sulfhydryl-containing component having  $m$  sulfhydryl groups, and the second component, component "B," is a sulfhydryl-reactive component B having  $n$  sulfhydryl-reactive groups capable of reaction with the  $m$  sulfhydryl groups to form covalent bonds, wherein  $m \geq 2$  and  $n \geq 2$ , and generally the sum of  $m+n \geq 4$ . Preferably, at least one of  $m$  and  $n \geq 3$ , and more preferably,  $m$  and  $n$  are each  $\geq 4$ ; in this way, sufficient reactivity for rapid formation of a three-dimensional polymeric gel is ensured. For extremely fast-reacting compositions, both  $m$  and  $n$  are each  $\geq 12$ . The compositions may be used either in situ or ex situ, to give a biocompatible crosslinked gel having utility in a host of different contexts, e.g., in bioadhesion, biologically active agent delivery, tissue augmentation, and other applications. The preferred context, however, involves crosslinking and gelation in situ.

The reaction conditions necessary for the rapid crosslinking reaction to take place will depend on the particular components A and B. When neither component is a liquid at room temperature, the reaction must be carried out in an added solvent, preferably a sterile aqueous medium. If at least one of the components is a liquid and capable of serving as a reaction solvent, the reaction may be conducted "neat" (also referred to as "in bulk"), i.e., no added solvent is necessary. In addition, for components that crosslink via a nucleophilic substitution mechanism, such that covalent bonds are formed by nucleophilic attack of the sulfhydryl groups on electrophilic sulfhydryl-reactive groups, an added base is typically necessary to increase the nucleophilicity of the sulfhydryl groups such that the crosslinking reaction occurs sufficiently rapidly. For components that crosslink via other mechanisms, an added base is generally not required (although one may be present). For example, reaction of unconjugated olefins with sulfhydryl groups does not involve nucleophilic substitution, but rather requires light or other radiation effective to generate the sulfhydryl radical R—S—, and a suitable free radical initiator.

The components of the composition will generally be admixed, under the reaction conditions appropriate to promote rapid crosslinking of the selected components, e.g., in bulk, in an aqueous liquid, with added base, and/or in the presence of radiation and/or a free radical initiator), immediately prior to administration. Alternatively, the components may be individually applied to the site of administration under appropriate reaction conditions, such that admixture occurs at the administration site.

It will be appreciated that more than one sulfhydryl-containing component and/or more than one sulfhydryl-reactive component may be present in the reactive composition.