

## IN SITU POLYMERIZABLE HYDROGELS

## FIELD OF THE INVENTION

The present invention relates generally to the in situ formation of hydrogels, and more specifically, to compositions of hydrogels that are formed in situ by a combination of physical and chemical crosslinking.

## BACKGROUND OF THE INVENTION

Hydrogels are materials which absorb solvents (such as water), undergo rapid swelling without discernible dissolution, and maintain three-dimensional networks capable of reversible deformation. Hydrogels have been proposed for use in a number of medical applications, including barriers to prevent post-surgical adhesion, as tissue adhesives, as bone implants, and for occluding naturally-occurring and iatrogenically formed lumens.

Hydrogels may be either uncrosslinked or crosslinked. Crosslink formation in polymers is usually accompanied by an increase in viscosity due to an increase in apparent or real molecular weight, and often may result in the formation of a gelled state.

Polymers may be crosslinked by either physical or chemical means. Physical crosslinking differs from chemical crosslinking in that the linkages are typically weaker, of lower energy, and often reversible. Thus, physically crosslinked hydrogels often are deformable mechanically. Four fundamental forces have been found to be responsible for producing physical crosslinking: ionic interactions; hydrophobic interactions; hydrogen bonding and Van der Waals forces.

Gel forming compositions for use in preventing post-surgical adhesion are known. For example, U.S. Pat. No. 4,994,277 to Higham et al. describes a barrier to prevent post-surgical adhesions formed from a water soluble xanthan gum gel. The water solubility of the gel may lead to inadequate retention duration, and risk of displacement and migration.

U.S. Pat. No. 4,911,926 to Henry et al. describes methods and composition for reducing post-surgical adhesions by using aqueous and non-aqueous compositions comprising polyoxyalkylene block copolymers that form gels in the biologic environment.

The hydrogels described in the foregoing patent form weak physical crosslinks that give the gels a paste-like consistency at physiological temperatures. Because the resulting gels are not covalently crosslinked, however, they have no mechanical integrity and may be readily displaced from the application site.

U.S. Pat. No. 5,126,141 to Henry describes compositions and methods for reducing post-surgical adhesions with thermo-irreversible gels of polyoxyalkylene polymers and ionic polysaccharides. Both the polyoxyalkylene and ionic polysaccharide are crosslinked by physical crosslinks; no covalent crosslinking is disclosed.

Other gel forming compositions for use in preventing post-surgical adhesion have included: (a) chitin derivatives (U.S. Pat. No. 5,093,319) (b) chitosan-coagulum (U.S. Pat. No. 4,532,134); and (c) hyaluronic acid (U.S. Pat. No. 4,141,973). There is no clear mechanism for degrading these tonically crosslinked materials, or their constituent molecules, which may remain within the body for uncertain periods of time.

Likewise, U.S. Pat. No. 5,266,326 to Barry et al. describes in situ modification of alginate to form a hydrogel spinal

implant in vivo. Ionically crosslinked polysaccharides such as alginate are not absorbable in humans since no enzyme exists in humans to degrade the  $\beta$  glycosidic linkages. Also, the high molecular weight of the alginates used (upwards of 200,000 Da) does not allow filtration through the kidneys.

Covalently crosslinked hydrogels have been prepared based on crosslinked polymeric chains of methoxy poly(ethylene glycol) monomethacrylate having variable lengths of the polyoxyethylene side chains. The interaction of these hydrogels with blood components is reported in Nagaoka, et al., in *Polymers as Biomaterial* (Shalaby et al., Eds.) Plenum Press, 1983, p. 381.

U.S. Pat. No. 5,573,934 to Hubbell et al. describes ethylenically unsaturated water soluble macromers that can be crosslinked in contact with tissues, cells, and bioactive molecules to form gels. The patent does not describe the inclusion of physically crosslinkable components to facilitate in situ formation of hydrogels.

U.S. Pat. No. 4,740,534 to Matsuda et al. describes surgical adhesives comprising urethane prepolymers used in combination with an unsaturated cyano compound containing a cyano group attached to a carbon atom, such as cyano(meth)acrylic acids and esters thereof.

U.S. Pat. No. 4,804,691 to English et al. describes a method of making an adhesive that is polymerized in situ to join soft living tissue, including steps of preparing a hydroxyl-terminated polyester by reacting a biodegradable monomer with a polyhydroxy polymerization initiator. When applied to the moist soft tissue, the adhesive reacts with water to yield a cured adhesive having a resorbable backbone with urethane linkages. The adhesive is not water soluble, however, and thus cannot intimately mix with tissue fluids. Also, because the adhesive reacts with water, it cannot be applied as an aqueous solution or suspension, and has poor adherence in the presence of excess surface moisture on tissue.

U.S. Pat. No. 5,462,976 to Matsuda et al. describes in situ polymerizable tissue barriers formed from photocurable glycosaminoglycan derivatives that are water soluble in their precursor form. These materials require external energy sources for transformation and polymerize slowly. U.S. Pat. No. 5,410,016 to Hubbell et al. describes biodegradable hydrogels that polymerize more rapidly by a photoinitiated free radical polymerization from water soluble macromers.

Synthesis and biomedical and pharmaceutical applications of absorbable or biodegradable hydrogels based on covalently crosslinked networks comprising polypeptide or polyester components as the enzymatically or hydrolytically labile components, respectively, have been described by a number of researchers. See, e.g., Jarrett, et al., "Bioabsorbable Hydrogel Tissue Barrier: In Situ Gelation Kinetics", *Trans. Soc. Biomater.*, Vol. XVIII, 182 (1995); Sawhney et al., "Bioerodible Hydrogels Based on Photopolymerized Poly(ethyleneglycol)-copoly( $\alpha$ -hydroxy acid) Diacrylate Macromers", *Macromolecules*, 26:581-587 (1993); Park, et al., *Biodegradable Hydrogels for Drug Delivery*, Technomic Pub., Lancaster, Pa., 1993; Park, "Enzyme-digestible Swelling Hydrogels as Platforms for Long-term Oral Drug Delivery: Synthesis and Characterization", *Biomaterials*, 9:435 (1988). None of these references suggest the desirability of providing physical crosslinking in addition to chemical crosslinking to improve hydrogel formation in situ.

Several previously known chemical systems are compatible with carrying out chemical reactions or crosslinking in vivo to form covalently crosslinked hydrogels. Monomers or macromers usable to form hydrogels by chemical crosslink-