

such as β -aminopropionitrile (β APN), matrix inhibitors, antibodies, cytokines, integrins, thrombins, thrombin inhibitors, proteases, anticoagulants and glycosaminoglycans.

[0015] A process in accordance with the present invention involves mixing water with the PVA crystal to obtain a non-dehydrated PVA hydrogel, thereby eliminating the dehydration step prior to implantation. More specifically, the present invention involves freezing and thawing the PVA/water mixture to create an interlocking mesh between PVA polymer molecules to create the PVA hydrogel. The freezing and thawing step may be performed at least twice, with mechanical strength of the PVA hydrogel increasing each time the freezing and thawing step is performed. The process may include the further steps of pouring the PVA/water mixture into a mold, freezing the mixture, and the thawing the mixture to obtain a non-dehydrated construct. Additionally, the process may also include the step of removing the construct from the mold, immersing the construct in water, freezing the construct while immersed in water and thawing the construct while immersed in water to increase the mechanical strength of the construct. The process may also include the steps of adding bioactive agents to the hydrogel.

[0016] Because it can be manufactured to be mechanically strong, or to possess various levels of strength among other physical properties, it can be adapted for use in many applications. The hydrogel also has a high water content which provides desirable properties in numerous applications. For example, the hydrogel tissue replacement construct is especially useful in surgical and other medical applications as an artificial material for replacing and reconstructing soft tissues in humans and other mammals. Soft tissue body parts which can be replaced or reconstructed by the hydrogel include, but are not limited to, vascular grafts, heart valves, esophageal tissue, skin, corneal tissue, cartilage, meniscus, and tendon. Furthermore, the hydrogel may also serve as a cartilage replacement for anatomical structures including, but not limited to an ear or nose. The inventive hydrogel may also serve as a tissue expander. Additionally, the inventive hydrogel may be suitable for an implantable drug delivery device. In that application, the rate of drug delivery to tissue will depend upon hydrogel pore size and degree of intermolecular meshing resulting from the freeze/thaw device. The rate of drug delivery increases with the number of pores and decreases with an increasing degree of intermolecular meshing from an increased number of freeze/thaw cycles. The inventive hydrogel may consist essentially of a PVA polymer and about 20% to about 95% water, by weight. The mechanical and thermal properties of PVA hydrogel constructs, for biomedical applications in particular, are important to the performance of the constructs, as are the hydrogel's swelling properties and coefficient of friction. The structures produced by the novel process of this invention have advantageous properties in each of these areas. The process of the present invention produces crystallites in the PVA hydrogel polymer which leads to unique and enhanced mechanical properties, thermal behavior and increased fatigue strength.

[0017] The tensile properties of the PVA hydrogel of the present invention may be characterized by its deformation behavior. The freedom of motion of the PVA polymer of the present invention is retained at a local level while the network structure produced by the process of this invention prevents large-scale movements or flow. Rubbery polymers

tend to exhibit a lower modulus, or stiffness, and extensibilities which are high. Glassy and semi-crystalline polymers have higher moduli and lower extensibilities. The tensile and compressive properties of the construct of the present invention are reflected by a modulus of elasticity of between about 0.1 and about 20 megaPascals, thus producing a hydrogel having excellent strength and flexibility characteristics.

[0018] In the liquid or melt state, a non-crystalline polymer possesses enough thermal energy for long segments of each polymer to move randomly, called Brownian motion. As the mixture cooled, the temperature is eventually reached at which all long range segmental motion ceases. This temperature at which segmental motions ceases, which is a function of both the polymer material and how it is processed, is called the glass transition temperature. Experimentally, this glass transition temperature is often defined by incrementally increasing the temperature of the hydrogel until sequential reaction begins and energy is absorbed. The glass transition properties of the PVA hydrogel construct provided by the method of the present invention is greater than about 40 degrees Celsius.

[0019] An integral part of the physical behavior of PVA hydrogel constructs here disclosed is their swelling behavior in water, because the process of this invention requires that the PVA be immersed in water in order to yield the final, solvated network structure. The thermodynamic swelling force is counter balanced by the retractive force of the hydrogel structure and, in the process of this invention, constrained by the mold in which the hydrogel is placed. These retractive forces of the hydrogel are described by the Flory rubber elasticity theory and its variations. Equilibrium is reached, in water and at a particular temperature, when the thermodynamic swelling force is equal to the retractive force. The swelling properties of the PVA hydrogel construct of this invention are such that the dimensions of the construct are increased by swelling by less than about 20%, and preferably less than about 5%, when immersed in water. Alternatively, the shrinkage is correspondingly less than 20%, and preferably less than about 5%. When the PVA hydrogel of this invention is used in applications such as biomedical applications, for example as a knee joint resurfacing agent, low friction is desirable. The construct of the present invention has a coefficient of friction of less than about 0.1. For a general description of the physical properties of polymers and their properties see, *Biomaterials Science an Introduction to Materials in Medicine*, Ratner, et al. (Academic Press 1996), pp. 52-53 and 62.

[0020] The hydrogel is especially suitable for vascular grafts and heart valve replacements, because the hydrogel is thromboresistant, and because of the particular mechanical and physiological requirements of vascular grafts when implanted into the body. The hydrogel may also be used for contact lenses, as a covering for wounds such as burns and abrasions, as a nerve bridge, as a ureteral stent, and in other applications wherein a mechanically strong material is preferred. Because of its low coefficient of friction, the hydrogel may also be used as a coating to reduce friction between surfaces, such as on a catheter.

[0021] Other objects, features and advantages of the present invention will become apparent upon reading the following specification, when taken in conjunction with the accompanying examples.