

Hydrogels: Artificial Cartilage

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Cartilage is that pliable material that sits in between bones that connects at joints and when there is any sort of tear, loss or damage to the tissue, the result is the rubbing of bones against each other (Batista et al., 2012). Damage to articular cartilage is irreversible and can lead to chronic symptoms simply because cartilage cannot repair or regenerate itself (Gonzalez and Alvarez, 2014). Patients with conditions like osteoarthritis and osteochondral defects often times have cartilage damage in addition to other rheumatological issues (Batista et al., 2012).

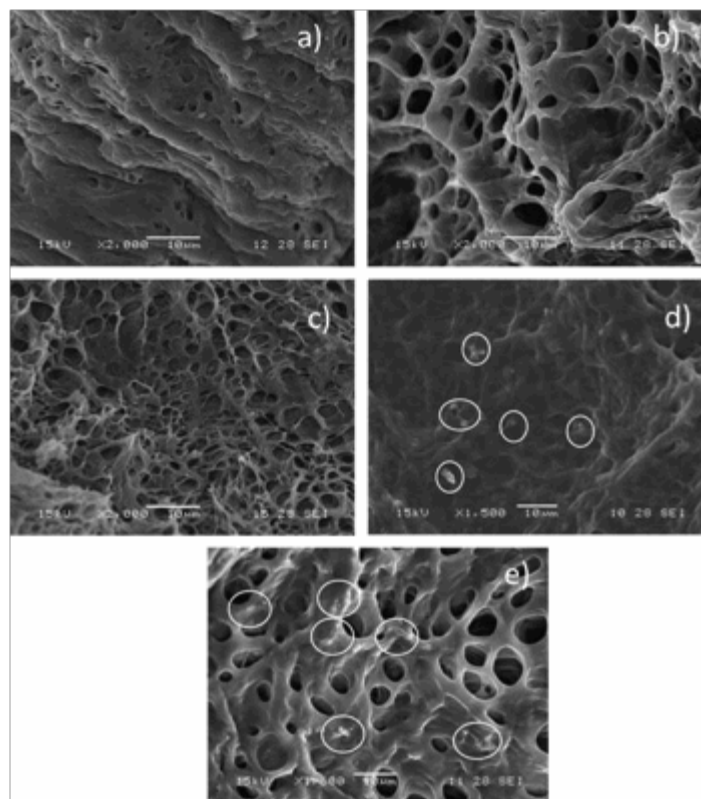
Despite the technological advances in biomaterials of recent years, a biotechnological cure for articular cartilage damage has not yet been discovered. Articular cartilage is composed of high-specialized, low friction tissue and has viscoelastic properties (Batista et al., 2012). One reason articular damage causes such great suffering is because cartilage has a low intrinsic ability to repair itself due to a lack of vascularization and due to low metabolic activity of mature chondrocytes, the cells necessary for differentiation and proliferation (Batista et al., 2012). Cartilage has two important functions: to transfer enormous forces evenly from one subchondral bone plate to another and to allow relative movement of the articulating surfaces with minimal friction and wear (Gonzalez and Alvarez, 2014). Cartilage is able to sustain high compression loads and high pressures, due to its morphological and biomechanical properties (Gonzalez and Alvarez, 2014). To create a technological system that could be implemented into a biological system and serve the functions of articular cartilage has been extremely challenging. One possible solution to this previously impossible medical challenge involves a system primarily composed of water. Currently, composite hydrogels, polymers crosslinked with hydrophilic ends and integrated with a unique bioactive filler, are being developed to reproduce the mechanical properties of articular cartilage and eventually integrate into surrounding tissue (Gonzalez and Alvarez, 2014).

While hydrogels have been used to treat and cure several conditions in the past, the hope is that a composite hydrogel has finally been designed that will mimic the mechanical properties and adhesive nature of articular cartilage and thus, help treat osteochondral defects (Gonzalez and Alvarez, 2014). Before there were any known medical uses for hydrogels within the last couple of years, a procedure known as microfracturing was performed to repair damaged cartilage (Gonzalez and Alvarez, 2014). During this quick procedure, tiny holes were drilled into the bone near the damaged cartilage, releasing blood and stem cells from the bone marrow into the area (Diaz, 2013). These cells were then expected to grow into healthy and normal cartilage. This did not occur, however. Because bone lacks a form of substrate, the new blood and stem cells did not have anything to hold onto and grew differently, creating scar tissue (Diaz, 2013). To avoid any consequences resulting from the weak and undependable properties of scar tissue, doctors have begun incorporating hydrogels into the microfracturing procedure to provide a sort of scaffold for the blood and stem cells to hold onto as they grow (Diaz, 2013). Once the holes are drilled, the hydrogel is applied to the holes and solidified with light (Diaz, 2013). In fact, the hydrogel becomes so integrated into the body that it actually dissolves as new cartilage grows (Diaz, 2013).

Creating a hydrogel that would demonstrate the physical, chemical, and mechanical properties of natural articular cartilage while suppressing its weak properties has been a grueling trial and error process. Variations in materials used and in doses of certain materials have been studied since recent advancements in biomaterials have been established. The polyvinyl alcohol (PVA) hydrogel has proven to be the most suitable implantable medical material to replace cartilage due to its biocompatibility, low protein absorption properties and higher tensile strength (Baker et al., 2012). In addition to its application for cartilage repair and replacement, PVA hydrogels have also been developed to create contact lenses, artificial pancreases, and synthetic vitreous humors (Baker et al., 2012). PVA is a linear synthetic polymer produced by hydrolysis of polyvinyl acetate (Baker et al., 2012). This hydroxylation causes the polymer to be soluble in water and resistant to organic solvents (Baker et al., 2012). Because it is very soluble to water the PVA polymer must be physically crosslinked or chemically crosslinked with electron beam irradiation to form the hydrogel (Baker et al., 2012). The degree, at which the polymer is hydroxylated, polymerized, and crosslinked can all be

regulated in order to achieve desired properties. Once crosslinked, the materials develop the necessary structural stability needed in order for the hydrogel to be implanted into the body (Baker et al., 2012).

As additional studies of the PVA hydrogel have been performed, more evidence has accumulated regarding the insufficiency of the hydrogel, itself, to mimic the nature of articular cartilage. One particular group of scientists that studied the effects of PVA hydrogels on osteochondral defects in rat knees, found that the average creep modulus of the gel increased over time (Batista et al., 2012). Creep is the non-recoverable deformation or extension of a material when a continuous load is applied to it. The creep modulus is a function of the logarithm of time under a constant load (Geoffroy, 2004). This is why an increase in creep of the hydrogels implanted into the knees of rats resulted in moderate to severe tissue deformation when bearing a load (Batista et al., 2012). The same group also discovered increased concentrations of calcium and phosphate in the implant and attributed the absorption to the increase of creep over time (Batista et al., 2012). While PVA hydrogels resemble soft tissue in several physical ways, they lack low mechanical resistance and durability and the ability to integrate with surrounding tissue (Gonzalez and Alvarez, 2014). Because PVA hydrogels are not fit for cell attachment and proliferation, they lack the ability to fix themselves onto a living tissue (Gonzalez and Alvarez, 2014). One alteration in the manufacturing of this implant that has proven to increase its strength and ability to adhere is the addition of hydroxyapatite (HA) to the PVA gel to form a composite PVA/HA hydrogel. Hydroxyapatite is the main mineral component of bone and when it is mixed with PVA via emulsification, it creates a scaffold for cartilage regeneration (Baker et al., 2012). This bioactive filler component is synthetically obtained and used throughout medicine because of its similarity to the mineral phase of bone, its biocompatibility, and its adequate osteointegration (Gonzalez and Alvarez, 2014). The amount of HA added to the hydrogel can have drastic effects on its properties. While the addition of HA increases pore size and provides stability for the soft PVA matrix, higher concentrations of HA per PVA result in more aggregates of HA throughout the gel (Gonzalez and Alvarez, 2014). HA aggregates have shown to deteriorate mechanical properties of composite materials (Gonzalez and Alvarez, 2014). In an experiment testing the effects of 1.5, 3, 6, and 7.5 wt% of HA per 15 wt% of PVA, the 1.5HA gel proved the most optimal in terms of mechanical properties when compared to the other gels comprised of varying amounts of HA (figure 1) (Gonzalez and Alvarez, 2014). The 1.5HA sample showed an increase in degradation temperature, which indicates a good interaction between both components of the material (Gonzalez and Alvarez, 2014). Samples of higher HA content showed a rather constant degradation temperature—a property that coincides with high levels of aggregation and a poor interaction between PVA and HA (Gonzalez and Alvarez, 2014).



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Figure 1 depicts SEM images of five different hydrogel samples: (a) PVA (b) 1.5HA (c) 3HA (d) 6HA (e) 7.5HA. Each

image depicts the porous nature of the hydrogel that results from the addition of HA to the PVA gel. As the amount of HA per PVA sample increases, the number of HA aggregates also increases. Large aggregates of HA are circled in (d) and (e). Image (b), depicting the 1.5 PVA/HA hydrogel contains the least amount of aggregates and the best interaction between PVA and HA, making it the most optimal sample for osteointegration.

I believe that in the near future, PVA/HA composite hydrogels will be implemented into the joints of patients with varying forms of articular cartilage damage without hesitation. The system has been extensively studied for several years and finalizing a few more details seems to be the goal of current scientists and doctors. However, conducting research on the effects of hydrogel implants and analyzing results can be complicated and time consuming. Because the PVA/HA hydrogel has proven to be effective and has not caused any damage to the surrounding tissues, the focus of the future should be more on discovering the most constructive integration of the materials than on the materials used. One of the most recent studies published on the topic involves the coating of HA particles on specific assemblies of PVA fibers. This coating method results in a tunable surface exposure of HA on the PVA matrix and reinforces the anchoring of the composite hydrogel to subchondral bone plates, thus promoting osteointegration (Moreau et al., 2014). If no problems arise from this form of integration between hydroxyapatite and PVA, this particular method of construction could be the future of hydrogels as an osteochondral implant.

Integration of this composite hydrogel for clinical applications to treat cartilage damage seems very promising. Because cartilage cannot regenerate itself due to a lack of blood supply, there is a great demand for some sort of treatment for cartilage defects. The synthesis of science and nature in this form is unique and blurs the lines between biology and technology as the hydrogel dissolves in the body as natural cells are formed.

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