Injectable Poly(vinyl alcohol) Hydrogels for Nucleus Replacement

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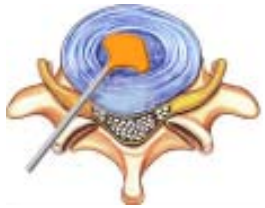

1. Replacing the deteriorating nucleus pulposus can preserve biomechanical function

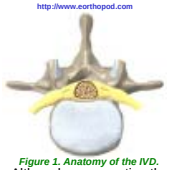

Figure 1. Anatomy of the IVD.

Intervertebral discs (IVDs) act as cushions mitigating and distributing the loads transferred along the spinal column. The disc's anisotropic structure gives it the ability to tolerate high compressive forces while providing support during tension, flexion and rotation, as well as protecting the fragile spinal nerve[1]. The inner viscoelastic material, termed the *nucleus pulposus*, is a natural hydrogel that occupies 20-40% of the total disc cross-sectional area and when healthy is composed of over 80% water. As the nucleus ages, it loses water, becomes less elastic and loses volume, causing the disc to shrink in height, compromising its biomechanical properties and function. This in turn can lead to herniated discs, abnormally loaded facet joints and pain and discomfort, but arguably the most serious consequence is the abnormal deformation and loading of the annulus (see Figure 2). Although conservative therapies work well for the majority of patients the long term prognosis is largely unknown and may lead to further degeneration with time (see Figure 3). A significant number of patients must undergo surgical intervention, which is usually invasive and often only partially successful over the long term. Nucleus replacement circumvents damage to other parts of the disc and offers a number of benefits for these patients in comparison to current therapies such as fusion and total disc replacement.

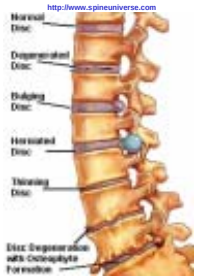

Figure 3. Effects of degenerative disc disease.

An ideal replacement for the damaged nucleus would be an incompressible, viscoelastic, space-filling and highly hydrated hydrogel similar to the healthy nucleus. Synthetic hydrogels can be tailored to possess mechanical properties similar to the natural nucleus. They contain large amounts of free water, which permits creep under compression and the ability to handle cyclical loading without loss of elasticity, similar to a natural nucleus. The water permeability of these materials allows diffusion of body fluids and nutrients into the disc space. A number of companies are working towards nucleus replacement devices with a variety of materials, but few have developed injectable materials. We present here a way to use hydrogels as an injectable nucleus replacement by controlling solvent quality[2]. This process affords a minimally invasive treatment for early forms of degenerative disc disease.

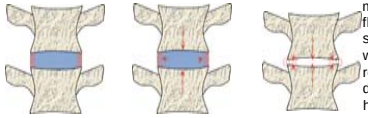

Figure 2. (a) Uncompressed, (b) compressed, and (c) abnormally compressed disc.

2. Injectable physically crosslinked PVA hydrogels have properties similar to the nucleus

Poly(vinyl alcohol) (PVA) is increasingly being considered as a biomedical material and has seen clinical success in a number of medical devices[3]. It is highly hydrophilic, elicits a low biological response[4], and is easily manufactured. PVA and copolymers have produced prostheses with mechanical properties similar to natural discs[5] and PVA has a swelling pressure that is very similar to that of the natural nucleus[6]. Although little clinical data is currently available for these materials in load-bearing applications, biomechanical testing of composite systems on cadaver joints has shown similar mechanical properties to natural discs[7].

Traditionally PVA hydrogels are manufactured through methods that use toxic crosslinkers or require ex vivo manufacture. We have developed a novel method using solution thermodynamics to allow injection of a PVA hydrogel without chemical crosslinkers.

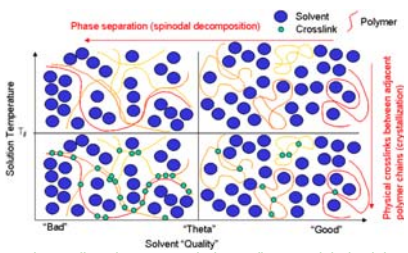

Figure 4. Effects of temperature and solvent quality on PVA chains in solution.

For a solution of PVA, two competitive processes can control PVA hydrogel formation: crystallization and spinodal decomposition (Figure 4). By a combination of these two processes, a hydrogel structure is formed. This novel solvent manipulation technique yields a thermodynamically unstable solution that is liquid under physiologically-relevant conditions and is therefore injectable. Once gelled it will form a highly hydrated, biologically inert hydrogel *in situ* with no reaction byproducts or exotherm. The gelation kinetics and final properties of the hydrogel can be manipulated by varying PVA concentration, solution temperature, and additives that change the solvent conditions ("gellants"). In this presentation we concentrate on poly(ethylene glycol) as a gellant because it is readily obtainable, biocompatible and approved for medical use.

3. Study Rationale: *In vitro* testing for validation of injectable PVA hydrogels

The aim of this study is to develop a range of *in vitro* testing methods that will allow validation of the properties of an injectable PVA-based hydrogel and demonstrate its value in the specific application of early intervention nucleus replacement. Specific concerns that must be addressed for an injectable nucleus can largely be described as "injectablility and gelation" and "survivability". Here we present *in vitro* evidence of the applicability of PVA hydrogels for injectable nucleus replacement applications. With the advent of the solvent manipulation technique described above there is now the ability to inject PVA percutaneously and form a gel in situ without the use of dangerous crosslinkers. Here we describe a range of novel tests, and the resulting outcomes, designed to validate this material before proceeding to more invasive animal models.

4. PVA pre-gel can be injected through a 16G needle to form a gel in situ

Denucleate disc with Hydrocision SpineJet® → Equilibrate spine segment in 40 °C water for 3-4 hours → Cool syringe of PVA pre-gel solution to 40 °C → Insert bleed needle into nucleus space → Inject PVA pre-gel solution through denucleation site → Equilibrate 24 hours at 40 °C → Dissect disc and examine hydrogel

In vitro and *ex vivo* models were developed to assess gelation of hydrogel formulations in as close to physiological conditions as possible. The *ex vivo* model validates hydrogel gelation in a sizeable disc space in a physiologically relevant aqueous environment by validating gelation after injection using a 16 G needle. The procedure is shown schematically above. Successful injection and gelation of the hydrogel solution is characterized by the presence of an opaque hydrogel that fills the nucleus space, as depicted in Figure 5b. An opaque, white viscoelastic hydrogel can be seen that fully fills the evacuated nucleus space.

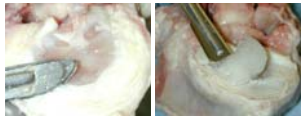

Figure 5. (a) Partially gelled PVA solution and (b) fully formed PVA hydrogel in ex vivo model.

5. PVA hydrogels can resist extrusion through a surgically created needle hole

Cool PVA pre-gel solution to 40 °C → Inject into extrusion hole → Equilibrate 15 minutes in 40 °C water → Compress fixture at 5 mm/min to 3 kN → Monitor force and gel behavior

Migration or expulsion of the gelled device from the nucleus space would cause significant surgical complications and has been seen in some early experiments by competitive product manufacturers. The procedure described here relies on a substantially intact annulus. The injected PVA hydrogel system must therefore resist extrusion through a surgically created or existing annular defect such as a tear or the needle entry point. To test extrusion resistance a 15 mm hydrogel is cast in a plunger type fixture with a 5 mm circular defect (Figure 6) following the scheme shown above. The parameters mimic a short set time for the hydrogel at physiological temperatures and a worst-case scenario extrusion hole.

Figure 7 presents load versus time curves for two representative hydrogel formulations that "fail" and "pass" in the static extrusion model. The inset images in the figure show that the formulation that failed the test permanently extruded from the 5 mm hole at loads below 700 N, exhibiting tearing as it exited the fixture. The hydrogel that passed the test did not extrude out the hole, but rather bulged slightly early in the test without further expulsion, and then retracted back in after testing.

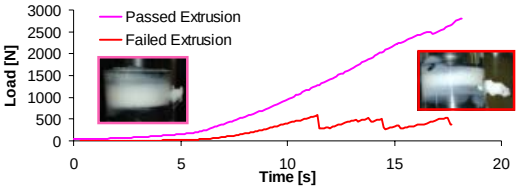

Figure 7. Load versus time curves for PVA hydrogels that pass and fail in static extrusion.

Figure 6. Static extrusion fixture.

6. An IVD fatigue model is used to examine the effects of cylic loading on PVA hydrogels

Cool PVA pre-gel solution to 40 °C → Inject into extrusion hole → Equilibrate 15 minutes in 40 °C water → Compress fixture at f = 1 Hz to 2.75 kN +- 0.25 kN

A novel fatigue model was developed based on a draft ASTM guidance document using a silicone rubber annulus (see Figure 8). The rubber has been suggested as a good analog for the annulus in compression. In this case, the rubber was manufactured with a 5 mm hole to mimic an annular defect. The entire assembly was mounted on an MTS mini-Bionix load-frame in a water bath held at 40 °C. The filter discs allowed exchange of water and gellant between the hydrogel and the water bath while still providing load support during compression. The hydrogel was equilibrated in the fatigue fixture as shown in the flow chart above. The composite hydrogel/rubber "disc" was then subjected to 500,000 loading cycles. The control was an empty annulus representing a denucleated disc. Preliminary results are shown in Figure 9. In all cases, the renucleated sample crept less than the denucleated sample, as would be expected. In addition, the complex modulus of the composite disc was also higher, implying that the renucleated disc is stiffer than the denucleated one. Upon test completion the fixture was broken apart and the material visually examined for debris generation, which was not evident. In addition, the samples were weighed and total solids content was verified. The final solids content of the hydrogel was 10% which is the expected mass ratio of PVA to water if the hydrogel had been allowed to swell freely. Although not considering flexion/extension, tension or rotation, this simple model suggests that the materials proposed can survive under the loading conditions experienced *in vivo* in the composite IVD.

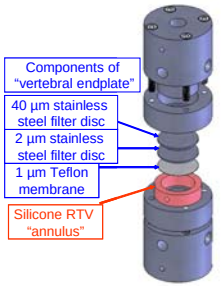

Figure 8. IVD fatigue model fixture.

7. PVA hydrogels meet the mechanical and physical needs of an injectable nucleus replacement

We have developed an injectable nucleus replacement using PVA by controlling the crystallization and spinodal decomposition of PVA solutions. This material is biocompatible (cytotoxicity and endotoxicity data not shown) and has been successfully loaded with radiopacifiers (not presented here). We have shown that this solvent manipulation technique yields hydrogels that can be readily injected through a 16 G needle and that gel successfully in the intervertebral disc in a benchtop animal model. The gels also resist static extrusion at loads up to three times body weight, indicating that the formulations are unlikely to suffer from extrusion or expulsion issues *in vivo*. Finally, we have shown early data assessing the hydrogel's fatigue properties over extended periods of time. Current results suggest that the hydrogel remains in the nucleus space under cyclic loading and does not mechanically deteriorate, or generate debris over 500,000 cycles at loads near three times body weight. Although more physiologically relevant fatigue tests must be performed, these early data strongly suggest that this hydrogel will perform well in a relatively intact annulus fibrosus. In the future we intend to extend the length of fatigue testing, with more physiologically relevant loads as a preliminary step towards *in vivo* porcine model safety testing.

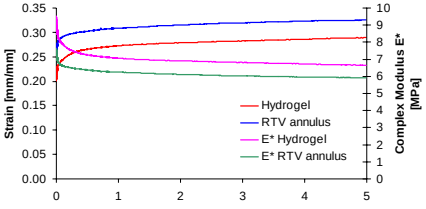

Figure 9. Preliminary fatigue results for RTV control annulus and composite hydrogel/RTV disc.

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