Review

A review of polyvinyl alcohol and its uses in cartilage and orthopedic applications

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Abstract: Polyvinyl alcohol (PVA) is a synthetic polymer derived from polyvinyl acetate through partial or full hydroxylation. PVA is commonly used in medical devices due to its low protein adsorption characteristics, biocompatibility, high water solubility, and chemical resistance. Some of the most common medical uses of PVA are in soft contact lenses, eye drops, embolization particles, tissue adhesion barriers, and as artificial cartilage and meniscus. The purpose of this review is to evaluate the available published information on PVA with respect to its safety as a medical device implant material for cartilage replacement. The review includes historical clinical use of PVA in orthopedics, and *in vitro* and *in vivo* biocompatibility studies. Finally, the safety recommendation involving the further development of PVA cryogels for cartilage replacement is addressed. © 2012 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 00B:000–000, 2012.

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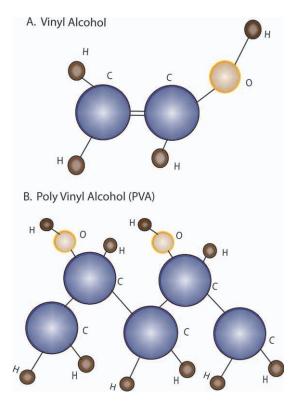
INTRODUCTION TO POLYVINYL ALCOHOL

Polyvinyl alcohol (PVA) is a linear synthetic polymer produced via partial or full hydrolysis of polyvinyl acetate to remove the acetate groups (see Figure 1). The amount of hydroxylation determines the physical characteristics, chemical properties, and mechanical properties of the PVA.[1] The resulting PVA polymer is highly soluble in water but resistant to most organic solvents. The higher the degree of hydroxylation and polymerization of the PVA, the lower the solubility in water and the more difficult it is to crystallize.[2] Due to its water solubility, PVA needs to be crosslinked to form hydrogels for use in several applications. The crosslinks, either physical or chemical, provide the structural stability the hydrogel needs after it swells in the presence of water or biological fluids.[3] The degree of crosslinking dictates the amount of fluid uptake, and thus the physical, chemical, and diffusional properties of the polymer, and ultimately its biological properties (see Figure 1).

Techniques such as "salting out" polymer gelation have been shown to form stable PVA hydrogels using different molecular weights and concentrations.[4] These molecular weight and concentration differences have an effect on swelling and Young's modulus.[4] Soft hydrogels with as little as 10% polymer, or stiff hydrogels of 50%–60% polymer are possible, thereby spanning the properties of most soft tissues.

PVA's resistance against organic solvents and aqueous solubility makes it adaptable for many applications.[1,2] PVA is commonly used in the textile industries, for paper products manufacturing, in the food packaging industry, and as medical devices. PVA is used as an industrial and commercial product due to its low environmental impact, which includes its high chemical resistance, aqueous solubility, and biodegradability. FDA has approved PVA to be in close contact with food products; in fact, PVA films exhibit excellent barrier properties for food packaging systems. In medical devices, PVA is used as a biomaterial due to its biocompatible, nontoxic, noncarcinogenic, swelling properties, and bioadhesive characteristics.[5] Table I identifies some implant and nonimplant devices currently made of different forms of PVA.

The purpose of this review is to evaluate the available published information on PVA with respect to its safety as a medical device implant material. Recently, Alves et al.[4] reviewed the biomaterials applications of PVA, focusing on its supramolecular properties and their effects on the macroscopic properties of the material. This review addresses the use of PVA for cartilage and orthopedic applications. The review includes historical clinical use of PVA in orthopedics, and *in vitro* and *in vivo* biocompatibility studies.

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FIGURE 1. A: The structure of vinyl alcohol is shown. B: PVA is synthesized by the hydrolysis of polyvinyl acetate. The structure of PVA is shown in this figure. Typical levels of hydrolysis are from 80% to greater than 99%, with PVA hydrogels formed from nearly fully hydrolyzed forms. PVA hydrogels are formed from crosslinking of the linear polymers resulting in polymer (gel)–fluid (sol) with tunable properties. At low polymer content, fluid freely moves through the matrix resulting in a soft compliant material. Increasing polymer content significantly stiffens and strengthens the matrix [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

HISTORICAL USE OF PVA FOR MEDICAL DEVICES

PVA hydrogels and membranes have been developed for biomedical applications such as contact lenses,[6] artificial pancreases,[7,8] hemodialysis,[9] and synthetic vitreous humor,[10] as well as for implantable medical materials to replace cartilage[11–16] and meniscus tissues.[17,18] It is an attractive material for these applications because of its biocompatibility and low protein adsorption properties resulting in low cell adhesion compared with other hydrogels.

PVA shows higher tensile strength and elongation before breaking than hydrogels such as polyhydroxyethyl methacrylate,[6,19] making PVA a suitable hydrogel for soft contact lenses, extending wearing time without inducing hypoxia to the cornea.[6]

Low-temperature crystallization of PVA with a water miscible organic solvent has been used to produce a hydrogel with high tensile strength, high water content, and low protein adsorption,[19] further improving its use as a lens material. PVA has also been used in combination with polyethylene glycol and hydroxypropyl methylcellulose, increasing content for medical applications such as artificial tears.

In addition to its use in nonimplanted medical applications, PVA is used in several medical devices that are implanted in the body. Particulate PVA has been used to treat vascular embolisms,[20,21] hydrophilic coatings to improve neurologic regeneration,[22] and as tissue adhesion barriers.[23–25] These diverse uses of PVA in medical devices indicate that it is safe for human use in applications where adsorption of host protein is undesired and the device experiences tensile stress during use.

PVA's properties also make it a good biomaterial candidate for simulating natural tissues inside the body, such as cartilage[11–14,16,26,27] and meniscus.[17,18] The following sections will review PVA implants for cartilage replacement applications.

PVA FOR CARTILAGE REPLACEMENT IN ARTICULAR AND MENISCAL APPLICATIONS

Cartilage lacks vascularity, and its cellular components, chondrocytes, have low mitotic ability, making it a particularly difficult tissue to repair or regenerate.[27] Cartilage is the prototypical, biologic hydrogel composed of ∼60%–80% water with its mass balance being mostly collagen and glycosaminoglycans. PVA hydrogels have been investigated for replacement of damaged cartilage due to their high water content, as well as their elastic and compressive mechanical properties. PVA cryogels used in cartilage resurfacing are prepared from high concentrations of high-molecular weight polymers (generally 30% PVA or higher). These PVA

TABLE I. Uses of PVA in Implantable and Nonimplant Devices

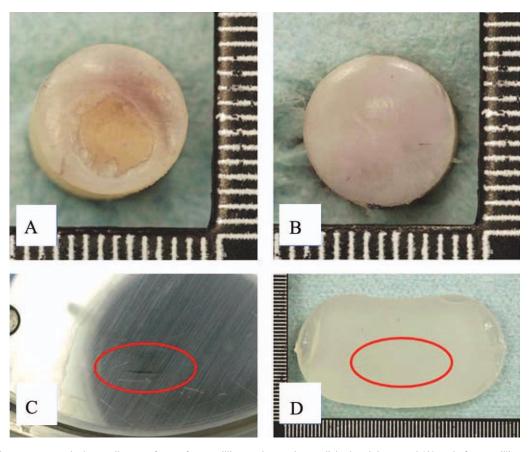| Device Type	Product	PVA Form	Patient Contact
Nonimplant devices	Surgical sponges and packing	Polymeric open cell foam	Transient to short-term wound packing
	Eye wetting drops	Polymer in solution	Short-term contact, direct application to eye tissues
	Contact lenses	Molded polymer hydrogel	Short-term contact, direct application to eye tissues
Implantable devices	Hydrophilic coatings (catheters, leads, etc.)	Polymeric over coating	Transient to long-term implant, blood contact
	Vascular embolic agents	Polymer hydrogel microspheres	Permanent implant, blood contact
	Tissue adhesion barriers	Polymer hydrogel sheets	Permanent implant, blood contact
	Nerve guides	Polymer hydrogel tubes	Permanent implant, nervous tissues
	Cartilage replacements	Molded polymer hydrogel	Permanent implant, blood and bone contact

FIGURE 2. Wear seen on articular cartilage surfaces after 1 million cycles against polished stainless steel (A) and after 1 million cycles against PVA hydrogel matrix (B). Articulation zones are highlighted in (C) and (D), respectively. Severe cartilage wear damage is observed with articulations against stainless steel as opposed to articulating against the PVA hydrogel surface. (Figure 2 is courtesy, Carticept Medical) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

cryogels have water contents similar to the surrounding healthy cartilage and when prepared from saline are osmotically balanced with the fluids and tissues within the joint space. Bray and Merrill[28] were one of the first groups to report the use of PVA for articular cartilage repair in the early 1970s. There are many other researchers who followed and studied PVA as an artificial cartilage repair[11–16,29]; we will address some of them below.

Articular cartilage consists of a lubricated, avascular tissue with high water content and mechanical tensile strength of 17 MPa[30] and compressive modulus varying between 0.53 and 1.82 MPa.[31] An ideal implant replacement for cartilage would mimic this structure, mechanical properties, and composition. Total joint replacement and total shoulder arthroplasty are commonly performed using polyethylene and/or metallic materials (titanium, chromium, etc.), which are both stiffer than cartilage and do not have lubrication, shock absorption, and deformation properties of native cartilage. Although they are suitable as joint replacement devices, not all cartilage defects require radical tissue removal to achieve restoration of function.

PVA hydrogels have been investigated as artificial cartilage replacements due to their rubber elastic physical properties, and because the hydrogels can be manufactured to have tensile strength in the cartilage range of 1–17 MPa[14]

and compressive modulus varying from 0.0012 and 0.85 MPa depending on the polymer concentration and number of cycles tested.[32]

Wear properties

Major reasons that orthopedic implants fail are osteolysis and aseptic loosening due to wear. Wear debris causes biological responses by activating macrophages, followed by the release of inflammatory agents that may lead to bone resorption and loosening of the implant.[33] In many cases, the wear debris volume is not the determining factor for the biological response, but rather the amount of wear particles that are within the critical size range of 0.2 to 0.8 μm, which will activate the macrophages.[33,34] It has been shown that *in vitro* testing of wear particles does not always resemble the size and volume of wear particles *in vivo*.[34] Therefore, a key question when investigating a new implantable material is the effect of its wear particles *in vivo*.

Suciu et al.[35] investigated PVA's wear characteristics as an artificial cartilage replacement for knee joint reconstruction. It was concluded that the thicker the PVA layer for cartilage tissue replacement, the lower the wear factor. Also, the composition of the PVA made a difference in wear resistance; the lowest water content produced the smallest wear factor. A comparison of PVA wear particles with

TABLE II. Biomechanical Properties Comparison for Cartilage Versus PVA Hydrogels

Physical Property	Articular Cartilage	PVA Hydrogel[a]
Unconfined compression–compressive modulus	Typical range: 0.31–0.80 MPa	Low load modulus: 2.56 MPa High load modulus: 3.68 MPa
Confined compression–aggregate modulus	Typical range: 0.60–1.21 MPa Behavior to compressive loading is biphasic	7.36 MPa Behavior to compressive loading is biphasic
Shear–shear modulus	Typical range: 0.28–0.54 MPa	0.46 MPa
Compressive creep–creep and creep recovery	Behavior to compressive creep was biphasic Minor permanent set under extreme compressive loading	Behavior to compressive creep was biphasic Minor permanent set under extreme compressive loading
Coefficient of kinetic friction	Typical range: < 0.01–0.05 (cartilage against cartilage)	0.04–0.07 (PVA hydrogel against cartilage)

[a] Observed values for 40% PVA hydrogel matrix.

ultrahigh molecular weight polyethylene (UHMWPE) particles indicated that PVA caused less inflammation than UHMWPE.[29] Other studies have found that PVA hydrogels have the highest wear factor when it is adjacent to stainless steel, rather than natural cartilage.[36]

Carticept Medical also performed *in vitro* studies on five cartilage plug samples against stainless steel and PVA surfaces. Wear analyses included visual inspection and scoring of the cartilage surface damage (scoring was on a 0 to 3 scale, and visualization was enhanced with India ink). The opposing surface (stainless steel or PVA) was also inspected. Severe cartilage wear damage was observed with articulations against stainless steel as opposed to articulating against the PVA hydrogel surface after 1 million cycles. The results are shown in Figure 2.

Studies investigating the wear characteristics of PVA with polyvinyl pyrrolidone (PVA/PVP) using a six station pin on disc machine were done to determine effects on friction and wear characteristics.[37] Wear was only observed in the back side, or the nonarticulating surface, of the PVA/PVP hydrogel. The results indicated that the higher the polymer content, the lower the wear of the hydrogel.[37] Some factors investigated to improve the wear resistance of PVA-H for articular cartilage are the use of gamma irradiation[38] in doses higher than 50 KGy,[39] addition of crosslinking agents[40] and combination with other materials such as titanium.[12]

Mechanical properties

To simulate the compressive properties of native cartilage, the composition and the freeze/thaw process is controlled when preparing PVA cryogels.[14] In addition, due to their high water content, PVA cryogels exhibit biphasic mechanical properties with rapid water loss under initial compression analogous to normal articular cartilage, as well as a low coefficient of friction due to fluid-film formation on loading. Due to the similar osmotic, physical, and frictional properties of PVA cryogels to native cartilage, joint resurfacing repairs using these materials do not require replacement of the opposing articular surface. Cartiva® biomaterials (Carticept Medical) have similar mechanical properties to native cartilage.[14] The preparation process of Cartiva® includes a number of freeze/thaw cycles, which promotes a

mesh entanglement between the molecular of PVA creating a stronger mechanical material.[40] Other PVA hydrogels created for cartilage replacement are mixed with crosslinking agents, such as glutaraldehyde, or are made as composite materials to strengthen the material. The introduction of additives may decrease the biocompatibility and introduce toxic agents.[40]

Studies have determined that a 2–3 mm thick layer of PVA cryogel is sufficient to withstand the mechanical forces needed in orthopedic applications without failure.[16] Thinner cartilage replacements are favorable due to the possible lubricant films that can form in between the articular surfaces due to the extra space. This lubricant film can help protect the surface from wear and simulate properties of native cartilage.[16] Stammen et al.[14] concluded that Salubria® PVA hydrogel can have similar mechanical properties, shear, compressive and failure properties, as native articular cartilage without the addition of crosslinking agents or composite additives. Table II compares the biomechanical properties of articular cartilage and PVA hydrogel. Overall, PVA hydrogel has similar properties to articular cartilage showing 6× higher values of aggregate modulus under confined compression (*observed values for 40% PVA hydrogel matrix).

BIOCOMPATIBILITY OF PVA
Preclinical and clinical studies using PVA hydrogels

The biocompatibility of PVA implants was demonstrated by Tadavarthy et al.[21] in 1975 with the development of the Ivalon embolic material. PVA gels with 80%–90% water content by weight were implanted subcutaneously or intramuscularly into rabbits, and no adverse effects were noticed in the surrounding tissue leading to a confirmation of the biocompatibility of the material.[41] PVA hydrogel crosslinked by gamma irradiation has also been shown to function as a vitreous substitute. In these studies, PVA hydrogels were injected into the eyes of crab-eating macaques; after 3 months, there was no evidence of tissue loss, changes in opthalmoscopic findings, or increases in intraocular pressure.[10]

Biocompatibility of PVA particles used for vein embolization was studied by Covey et al.[20] in 58 patients, determining that the particles were safe and effective in achieving left hemi-liver hypertrophy. Nakamura et al.[42] studied

PVA-H in rats and reported the formation of a malignant tumor; this is one of the only reports with carcinogenesis results. It was noted by Nakamura that this carcinogenesis formation might be due to the high water content in PVA-H.

In the food industry, PVA's oral toxicity was reviewed by DeMerlis and Schoneker[43] concluding that PVA is an orally safe product to use. The LD_{50} reported was between 15 and 20 g/kg, indicating a low acute oral toxicity.

Further biocompatibility studies were addressed for PVA mixed with other materials. Hydroxyapatite (HA), the main mineral component of bone, was mixed with gelatin and PVA by emulsification to create a cartilage scaffold for tissue engineering. Wang et al.[44] studied this composite material in vivo by implanting it subcutaneously in the dorsal region of rats for 12 weeks. The results indicated that the composite scaffold HA/PVA/gelatin is biocompatible and may serve as a cartilage scaffold for tissue engineering applications.

Another group studied PVA mixed with carboxymethylated cellulose to form a PVA gel to use as an adhesion barrier.[25] Biocompatibility was evaluated in a rabbit sidewall model reporting no side effects, excellent adhesion prevention, and sufficient biocompatibility. PVA/chitosan combinations have been studied for several biomedical applications. A combination of chitosan and PVA crosslinked with genipin was reported biocompatible and nontoxic after in vitro examination.[45] A specific biomedical use for carboxymethyl chitosan and PVA combination has been studied as a drug delivery system implanted subcutaneously in rats, resulting in high drug concentration retention and no cytotoxicity or hemolysis.[46]

Preclinical and clinical studies using PVA hydrogels for orthopedic applications

In orthopedics, PVA implants have been used in meniscus and cartilage replacements. Kobayashi et al.[17,18] studied PVA hydrogel for the replacement of meniscus using a rabbit model. The PVA hydrogel implants were placed in the lateral compartment of one knee of female rabbits. A meniscectomy on the bilateral knee of the same rabbit was done as a control. Five rabbits were examined after 2 years, while the rest were examined at earlier time points. Results of the 2-years postoperative follow-up showed that the PVA hydrogel implants were intact, with no wear or dislocation seen. The PVA hydrogel implants were shown to be stable inside the body and prevented osteoarthritic change in the surrounding articular cartilage. PVA hydrogel was also implanted in white rabbits for up to 52 weeks as an artificial articular cartilage replacement resulting in low inflammatory responses and high in vivo biocompatibility.[26]

Oka et al.[29] studied the biological response of PVA hydrogels implanted into canine knee joints as an artificial osteochondral composite material. The results indicated that the PVA hydrogel composite replacement with titanium fiber mesh (to facilitate bone integration and implant fixation) caused minimal damage to the articular cartilage and menisci, when compared with replacement with hard materials.[29]

PVA hydrogel fabricated with saline (Salubria®, Salumedica, Atlanta, GA) has been used for cartilage replacement in human clinical studies as well.[26,47–50] Maiotti et al.[47] studied the effectiveness of these PVA hydrogel implants in 18 patients with a mean age of 56 over a period of 2 years. The average size of the focal chondral defects on the femoral condyles was ~1.8 cm². The MRI images revealed that the PVA hydrogel implants were retained within the implant site, and knees were fully functional after 2 years postimplantation. There were significant improvements in the Lysholm II and Tegner scores at 24 months after implantation. The authors concluded that advantages of using these implants rely on the ease of insertion and their relative availability, when compared with autograft or allograft tissue donor transplantation.

Another human study using PVA hydrogel Salubria® implants included 12 patients with chondral defects on the femoral condyles averaging 2.1 cm².[26] This study was followed up for a relatively short period of time (4 months) using MRI and two-level X-ray imaging. The results were successful as the implant was still in place after 4 months postoperation, and no loosening, dislocation, or synovialytic joint reaction was detected.[26] There are a few studies that report implant failure after using PVA hydrogel Salubria implants.[49,50] These human studies report that dislocation and implant loosening were the main causes of failure. Following clinical feedback, both the implant site and the method of insertion were revised. Before revision failures were accounted for insufficient radial compression to maintain pressure within the implant socket. Another hypothesis for failure included the fact that clinicians were implanting multiple devices close together in a single defect site causing them to be free floating and thus subject to expulsion with loading and time. It was noted that multiple implants will work as long as they are not touching each other at the surface or below the implant. These studies[49,50] were both done before 2006, before the implant method and instrumentation revision.

Another study treated 15 patients with PVA hydrogel implants (Cartiva®, Carticept Medical) and resulted in 13 successful outcomes at 1 year, with one case of loosening and one case of dislodgement.[48] Re-evaluation of the patients of this clinical study after 30 months of implantation resulting in an average increase in International Knee Documentation Committee (IKDC) knee score of 60% compared with the mean (Sciarretta FV, personal communication, April 7, 2011). The IKDC score is the standard scoring system used by clinicians to measure the function and symptoms of patients with knee conditions. MRI images from this study are shown in Figure 3. These studies done by Sciarretta used a revised instrumentation method to perform the procedures arthroscopically. No implant expulsions were noted. These results indicate that integration is not necessary for the device to be successful; isolated implants surrounded by high quality bone, a flush presentation, and about 10% radial compression (diameter of implant site about 10% smaller than implant diameter) improve outcome in vivo. More human studies need to be performed with longer follow-up periods and higher sample sizes to make strong conclusions.
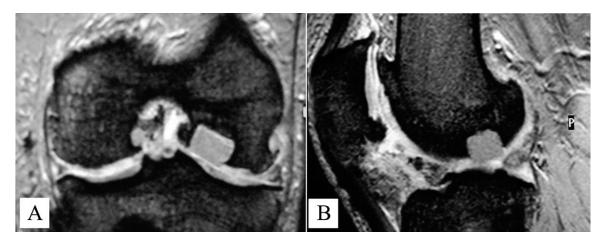
FIGURE 3. MRI of Cartiva® implants used in treating a focal defect in the femoral condyle. In a clinical evaluation of 65 patients, an average increase in IKDC knee score of 60% at mean follow-up of 30 months was seen (A: transverse section, B: sagittal section). (Figures courtesy of Carticept Medical)

CONCLUSIONS

PVA is a synthetic polymer that has been used for the past 30 years in several medical and nonmedical devices. Multiple nonclinical and clinical studies have demonstrated that PVA is a synthetic alternative to native cartilage replacement, and it is readily available compared with cartilage transplantation, which has limited availability and disease transmission concerns. Several animal and clinical studies using PVA for cartilage, meniscus, embolization, and vitreous solutions were discussed in this article, which demonstrate the biocompatibility and the safety related to this material. Follow-up periods of up to 2 years have been reported for animal and clinical studies, suggesting that PVA is stable and safe to use for medical devices. The biomechanical properties of PVA have also been investigated to better simulate the native tissue.

The PVA manufacturing process can be manipulated to generate the biomechanical properties desired. The thawing and freezing protocol, the addition of saline, crosslinking agents, and other materials all play a role in the biomechanical properties of the end product. Many investigators have also reported the wear characteristics of PVA. The *in vivo* studies have determined that wear particles from PVA are less harmful than wear particles from metals and other polymers such as UHMWPE as discussed previously.

In the treatment of focal defects, implant devices of PVA cryogel for the replacement of cartilage does not require significant removal of healthy tissue. The device can also articulate directly against opposing cartilage with no apparent damage. Therefore, PVA cryogels have faster recovery times and require less surgical trauma. Patients that undergo PVA cryogel plug surgery for chondral defects exhibit full knee movement right after surgery, and the knee can withstand full loads after 3 weeks. It was also determined that the surgical insertion method and the implant site have an effect on the success rate of PVA implants for cartilage replacement *in vivo*.

The extended literature reviewed in this article serves as a good summary of the *in vivo* studies using PVA throughout the years. There were no reports of synovitis or osteolysis in the clinical or animal studies reported. There are some reports on dislocation and loosening of PVA implants following cartilage replacement surgery. Misplacement of these implants was the major reason for dislocation and loosening. Multiple implants were placed at the same site, touching each other and causing expulsion. It was noted that these studies were done before the implant site and surgical instrumentation technique revisions. We conclude that PVA is a biologically compatible material that is stable *in vivo* (in both humans and animals) and has suitable biomechanical properties to be a promising material for future tissue replacement implants.

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