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Characterization of silver nanoparticle-infused tissue adhesive for ophthalmic use

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ABSTRACT

In this work, we demonstrate the successful enhancement of breaking strength, adhesive strength, and antibacterial efficacy of ophthalmic tissue adhesive (2-octyl cyanoacrylate) by doping with silver nanoparticles, and investigate the effects of nanoparticle size and concentration. Recent work has shown that silver nanoparticles are a viable antibacterial additive to many compounds, but their efficacy in tissue adhesives was heretofore untested. Our results indicate that doping the adhesive with silver nanoparticles reduced bacterial growth by an order of magnitude or more; nanoparticle size and concentration had minimal influence in the range tested. Tensile breaking strength of polymerized adhesive samples and adhesive strength between a T-shaped support and excised porcine sclera were measured using a universal testing machine according to ASTM (formerly American Society for Testing and Materials) standard techniques. Both tests showed significant improvement with the addition of silver nanoparticles. The enhanced mechanical strength and antibacterial efficacy of the doped adhesive supports the use of tissue adhesives as a viable supplement or alternative to sutures.

1. Introduction

Recently, silver nanoparticles (AgNPs) have been heavily examined as an antimicrobial additive in a wide variety of compounds and applications. Here, we investigate the potential for using AgNPs to imbue antibacterial properties for ophthalmic tissue adhesives. The eyes are subjected to various procedures and are potentially a site for infection and inflammation. For ocular surgeries, suturing corneas often produces asymmetrical healing that can result in astigmatism (Grinstaff, 2007). Tissue adhesives are being investigated as an alternative to conventional closure techniques in this surgical setting. To the authors' knowledge, this is the first such study to examine this application in the unique ocular environment.

Nanoparticles possess a large surface area to volume ratio, resulting in distinct physiochemical properties and unique antimicrobial interactions with bacteria and viruses (Gunasekaran et al., 2011). This geometric advantage has been leveraged in the development of pharmaceuticals, as it can be used to control the release rate and bioavailability of a variety of chemicals. Nanoparticle encapsulation has been

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used to create nanocolloidal suspensions of fluoroquinolones (Fresta et al., 1995) and novel antibacterials (Hamouda et al., 1999) which show significantly improved activity. A variety of metals have been tested as well, including copper, gold, silicon, zinc, magnesium, and silver (Hajipour et al., 2012).

The effects and efficacy of silver as an antimicrobial agent has been the subject of study for some time. Silver nanoparticles, as well as other metal oxide nanoparticles, are bactericidal because released reactive ion species can bind to the bacterial cell wall, alter cytoplasmic DNA and proteins, and modify enzymes involved in essential cellular processes (Gunasekaran et al., 2011; Li et al., 2012; Morones et al., 2005; Rai et al., 2009). Nanoparticles increase the antibacterial efficacy of Ag materials by providing a high surface area to volume ratio for molecular interaction of Ag^{+} ions with bacterial cell wall constituents (Marsich et al., 2013). AgNPs can be directed to the site of infection and have high bioavailability. The cytotoxic effects and mechanism of toxicity of metal oxide nanoparticles to eukaryotic cells remains an open question, however. There is evidence to suggest that NP cytotoxicity in eukaryotic cells is related to their ability to cross the cell membrane (Marsich et al., 2013), and that stabilizing AgNPs in a biocompatible matrix reduces eukaryotic cytotoxicity (Travan et al., 2011, 2009). Currently, silver compounds are applied in wound dressings for a variety of patients, but particularly for burns because of silver's antimicrobial properties (Ip, 2006; Lansdown, 2002a, 2002b). Compared to antibiotics, silver nanoparticles possess a multilevel antibacterial effect on cells and are highly effective against organisms that have developed a resistance to multiple drugs (Raghupathi et al., 2011).

Tissue adhesives are an alternative to conventional mechanical fasteners, and can be a safer and more efficient way of treating wounds. Tissue adhesives provide sufficient seal strength, a less traumatic closure, require no suture removal, are easy to use, and fast to apply (Duarte et al., 2012). Tissue adhesives can also be applied accurately in areas of the body where conventional fasteners cannot. Conventional mechanical fasteners such as sutures and staples are the current standard of care. They are relatively inexpensive and carry a low risk of allergic reaction or disease transmission. While they are effective wound closure techniques, they can damage tissues, resulting in infection and inflammation (Duarte et al., 2012). In 1998, the U.S. FDA approved a 2-octyl cyanoacrylate synthetic skin adhesive – Dermabond® – which has been widely adopted by surgeons and physicians for use in surgery and the emergency room. Other adhesive compounds used in this capacity include fibrin glues (Banitt et al., 2009; Pan et al., 2011), hydrogels (Grinstaff, 2007; Lee and Tsao, 2010; Zhou et al., 2012), collagen (Duarte et al., 2012), and biomimetic adhesives (Berdahl, 2009). Naturally derived tissue adhesives composed of fibrin or collagen can transmit disease or provoke a strong immune reaction via thrombin or fibrinogen if not properly screened. Synthetic tissue adhesives do not carry this risk (Duarte et al., 2012), though there are other factors, such as the potential for irritation, local toxicity, and scarring (Hida et al., 1988). Synthetic adhesives, such as polyurethane and cyanoacrylate, have demonstrated adhesive strength comparable to conventional mechanical fasteners, while other alternatives are still being characterized. The range of applications of modern adhesives – both FDA-approved and "off-label" – has expanded to many tissues in the body, including ophthalmic, cardiovascular, and orthopedic wounds and incisions (Aukerman et al., 2005; Duarte et al., 2012; Farion, 2003; Singer and Thode, 2004). With the addition of antibacterial properties, the expansion of approved uses is expected to continue.

Although tissue adhesives are intended to seal wounds from environmental bacteria, the presence of bacteria from an improperly cleansed wound allows continual growth of bacteria under the sealing adhesive layer. The addition of an antibacterial agent, such as parabens or silver nanoparticles, to tissue adhesives has previously been investigated. Ritterband et al. (2005) used a 2-octyl cyanoacrylate tissue adhesive with parabens to seal clear corneal cataract wounds. They speculate that the antibacterial properties of parabens could provide additional benefits in the closure of sutureless cataract surgery (Ritterband et al., 2005), but did not test this hypothesis to see if parabens impart antibacterial properties to the tissue adhesive. Romero et al. (2009) found that polymerization reaction of butyl-cyanoacrylate offers no antibacterial effect, ethyl-cyanoacrylate offers some antibacterial effect against some bacteria, but neither offers protection after polymerization.

This study focused on the infusion of silver nanoparticles into a 2-octyl cyanoacrylate synthetic tissue adhesive (Dermabond®) for ophthalmic applications. 2-octyl cyanoacrylate has been used as a high strength wound closure adhesive in various clinical settings, but no previous work investigated the effects of adding silver nanoparticles. We examined the effects of adding silver nanoparticles on the adhesive's antibacterial and mechanical properties. Specifically, we measured antibacterial efficacy, adhesive force, and breaking load of the doped adhesive using procedures defined or adapted from accepted ASTM (formerly American Society for Testing and Materials) standards. ASTM is an international organization that develops and publishes standard measurement methodologies and metrics. The FDA recommends ASTM standard methodologies – ASTM F2255-05, ASTM F2256-05, ASTM F2258-05, and ASTM F2458-05 – for bench-top testing of tissue adhesives for surgical wound closure as part of a process for device development and regulatory approval. Antibacterial efficacy was measured using the Kirby–Bauer disc diffusion assay and cell enumeration; inhibition halo diameter and colony forming unit (CFU) counts were collected and compared. Breaking strength was measured using a standard material strength test. Adhesive strength was measured between the force sensing platform and an excised porcine eye. All tests were performed for samples of 2-octyl cyanoacrylate with and without AgNPs at two different concentrations and two different nanoparticle sizes.

2. Materials and methods

The 4 nm and 10 nm diameter silver nanoparticles (NanoXact, from nanoComposix) were received as dried powders from the manufacturer and redispersed in 99.7+% chloroform (IBI Scientific) and 99.5+% anhydrous ethanol (Fisher Scientific), respectively, in accordance with manufacturer's specifications. 2-octyl