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Design of Hollow Hyaluronic Acid Cylinders for Sustained Intravitreal Protein Delivery

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ABSTRACT

A hollow cylinder intravitreal implant was developed to achieve sustained release of protein to the retina for the treatment of retinal diseases. Hollow cylinders were fabricated by molding and cross-linking hyaluronic acid, the major component of the vitreous humor. Hollow cylinders were filled with a concentrated protein solution, and the properties of the cylinder walls were tested. Cross-linked hyaluronic acid hydrogels with swelling degrees as low as 2.7 were achieved as a means to extend the release of protein. Hollow cylinders were capable of releasing an antigen-binding fragment for over 4 months at a maximum release rate of 4 μg per day. Protein release from hollow cylinders was modeled using COMSOL Multiphysics® software, and diffusion coefficients between 1.0×10^{-11} and 3.0×10^{-11} cm^2/s yielded therapeutically effective levels of protein. Cylinders with a 1 mm outer radius were capable of loading >1 mg of protein while releasing at least 2.5 μg a day for over 4.5 months. Although smaller cylinders facilitate intravitreal placement, decreasing the cylinder radius severely limited drug loading. Design of hollow cylinder intravitreal implants must balance high drug loading to reduce device size with control of the diffusion coefficient to sustain protein release.

Introduction

The increasing use of antibodies and protein in treating cancer, autoimmune diseases, viral infections, and even asthma has driven efforts to improve delivery systems.[1] In many cases, long-term, local delivery of proteins is preferred over parenteral routes to reduce systemic exposure and avoid frequent injections. Hydrogels offer a promising approach for many drug delivery applications because they can be formed into a variety of shapes and sizes, while at the same time exhibiting a wide range of permeabilities. However, one of the challenges of developing an effective hydrogel delivery device is maximizing drug loading while controlling the diffusion of proteins within the hydrogel to extend the release of proteins.

One particular area in which local, long-term delivery is needed is ocular drug delivery. Retinal diseases such as age-related macular degeneration (AMD) and diabetic macular edema (DME) require frequent injections into the vitreous to deliver drugs to the retina and prevent major vision loss. These diseases affect an estimated 16 million Americans and are the leading cause of blindness and vision loss in people over the age of 50 years.[2] Although a number of effective treatments have recently been developed, delivering these molecules to the retina remains a challenge. Vascular endothelial growth factor (VEGF) plays an important role in the development of new blood vessels, and elevated levels in the eye can lead to neovascularization that occurs behind the retina.[3] This can lead to abnormal growth and leakage of the choroidal vessels, which leads to macular degeneration and edema.[4] Both ranibizumab and aflibercept can prevent the signaling between VEGF and endothelial cells, but require intravitreal injections approximately every 4-8 weeks, which is unpleasant for the patient, expensive, and may lead to complications.[5,6]

A long-term, sustained delivery device would offer a number of advantages including convenience, safety, and financial benefits when compared to the current intravitreal dosing regimen. There are a number of drug delivery methods that have been developed to deliver long-term, sustained release to the retina including microspheres, implants, microcatheters, injectable depots, and even

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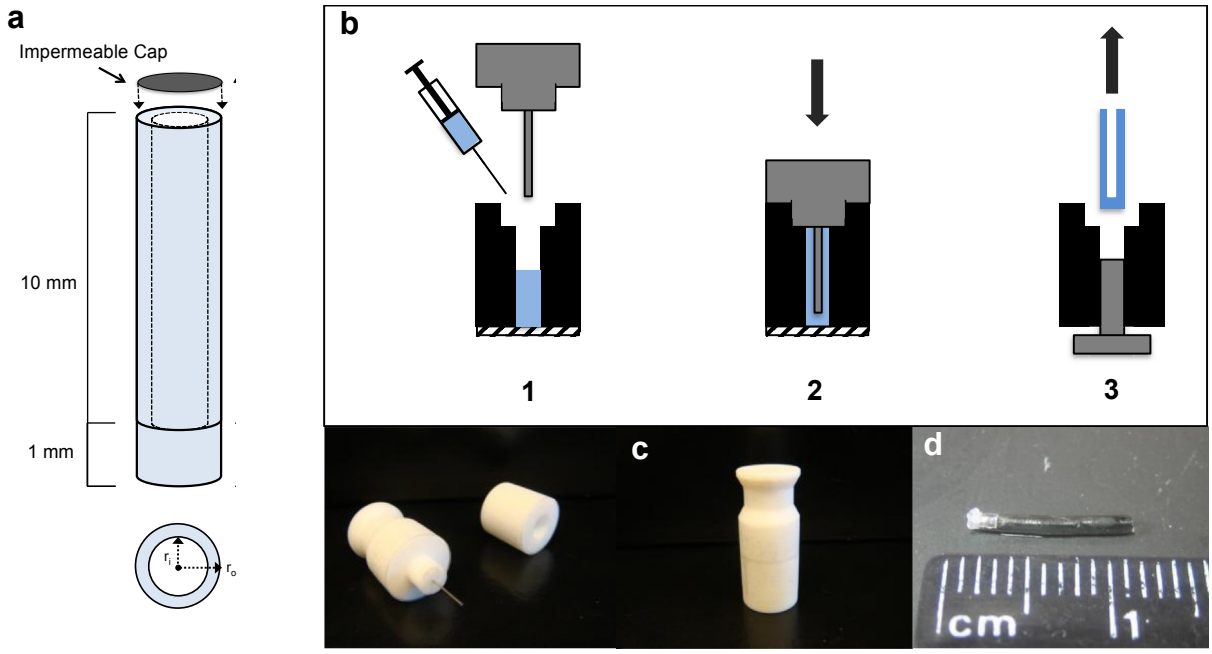

Figure 1. (a) Dimensions of the hollow cylinder implants. The outer diameter (r_o) was kept constant, and the wall thickness was varied by changing the inner radius (r_i). (b) Fabrication method used to create HA-DVS hollow cylinders. (1) HA-DVS solution is pipetted into a mold. A glass plate seals the bottom of the mold. (2) Upper cap is inserted into the mold while the cross-linking reaction occurs. (3) Both the upper mold and glass plate are removed and the finished hollow cylinders are removed from the mold using a custom plunger. (c) Hollow cylinder molds. (d) Capped hollow cylinder.

microneedles.[7-9] Of these methods, the one that has had the most clinical and regulatory success so far has been implants.[10] Early efforts focused on implants that were nonbiodegradable and made from a combination of polymers such as poly(vinyl alcohol), ethylene-vinyl acetate, and silicone.[11,12] Although these implants are excellent at controlling the release rate of small corticosteroids for an extended period of time, they have the downside of having to be surgically implanted and removed once the implant is depleted.[13] In an effort to reduce the amount of surgery needed, biodegradable implants using hydrophobic polymers such as polylactide and poly(lactide-co-glycolide) were developed.[14] An alternative option to hydrophobic polymer implants is hydrogels, which have been shown to be effective at delivering proteins.[15-18]

In this work, the use of hollow hyaluronic acid (HA) hydrogel cylinders was investigated for the sustained release of therapeutic proteins to the eye. As a significant component of the vitreous of the eye, HA is a logical choice for a hydrogel delivery system that would be implanted in the eye for long periods of time, where low toxicity and avoiding immunological responses are crucial for success.[19,20] As HA is used in a variety of different biomedical implants, a variety of strategies for cross-linking HA to achieve biodegradation *in vivo* at desired rates have been developed.[21-23]

A primary difficulty in developing an ocular implant is that the device must be small enough to be implanted in the eye, yet carry a large enough drug load to achieve long-term release at the desired level. Accomplishing this requires a highly cross-linked hydrogel that has a low swelling degree to produce the diffusion coefficients required to achieve extended release. However, achieving extended release from a polyelectrolyte gel such as HA is especially challenging, as such gels swell extensively in water, primarily due to the osmotic swelling pressure of the counterions,[24] and solute diffusion coefficients in highly swollen gels approach their values in solution.[25] Therefore, because of their high water contents, these polyelectrolyte gels typically release encapsulated drugs at relatively rapid rates due to the high solute diffusion coefficients.[26,27] HA hydrogels that are chemically or physically cross-linked often display release profiles that exhibit complete release in less than a few days, and in limited cases, up to a few weeks.[27]

In this article, HA was highly cross-linked with divinyl sulfone (DVS) to form hollow cylinders that were 1 mm in diameter and 10 mm in length. The relatively large size of the prototypes made loading, capping, and handling of the cylinders practical, while still being comparable to cylinder sizes that has gone under clinical trials for intravitreal drug delivery, albeit at the upper end of the range.[28,29] The effects of HA formulation, wall thickness, and concentration of protein within the hollow cylinder on the release rate were assessed by a combination of prototyping and simulations. Hollow HA cylinders with 3 different outer diameters (O.D.) were modeled: a 1 mm cylinder that would have to be implanted, a 0.45 mm cylinder that could be injected using a 22-gauge microinjector, and a 0.21 mm cylinder that could be injected using a 27-gauge needle. By using a variety of wall thicknesses and diffusion coefficients, a wide range of release rates and profiles were explored as design parameters.

Table 1
Simulation Parameters

Parameter	Description	Value
H	Height of gel	1 cm
R_o	Outer radius of gel	0.105-0.5 mm
R_i	Inner radius of gel	0.035-0.476 mm
$K = R_o/R_i$	Ratio of outer and inner radii	1-5
V_{load}[a]	Volume of loading cavity	0.03-6.4 μL
M_w	Molecular weight of drug	66,000 g/mol
C_0	Initial concentration	160 mg/mL
M_t	Mass released at time t	2-1026 μg
M_∞	Total mass released	2-1026 μg
D_{gel}	Diffusion coefficient in the gel	1×10^{-10} to 1×10^{-12} cm^2/s
D_{inner}	Diffusion coefficient in the inner volume	1×10^{-7} cm^2/s
D_{outer}	Diffusion coefficient outside the implant	1×10^{-7} cm^2/s
L	Length of permeable portion of cylinder	0.9 cm

[a] Calculated using R_o and R_i.