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The capsule drug device: Novel approach for drug delivery to the eye

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ABSTRACT

Treatment of age-macular degeneration requires monthly intravitreal injections, which are costly and have serious risks. The objective of this study was to develop a novel intraocular implant for drug delivery. The capsule drug ring is a reservoir inserted in the lens capsule during cataract surgery, refillable and capable of delivering multiple drugs. Avastin® was the drug of interest in this study. Prototypes were manufactured using polymethylmethacrylate sheets as the reservoir material, a semi-permeable membrane for controlled delivery and silicone check valves for refilling. The device showed near-zero order release kinetics and Avastin® stability was investigated with accelerated temperature studies.

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1. Introduction

Age-related macular degeneration (AMD), the leading cause of blindness in the US, has two principal forms: "wet" or exudative (characterized by angiogenesis or growth of new blood vessels), and "dry" or non-exudative (characterized by geographic atrophy and drusen, and a steady rate of progression to "wet" disease). In the US, there are over 2 million people with advanced AMD (expected to double by 2020), and worldwide, there are ~30 million people with this condition (Geroski & Edelhauser, 2000). While current anti-angiogenic modalities offer significant benefit to many patients with neovascular AMD, indefinite monthly intravitreal injections are costly due to the need for retina specialists, have serious risks (e.g., retinal detachment, endophthalmitis, hemorrhage, and cataractogenesis), and are, understandably, not well-accepted by patients.

Glaucoma is the leading cause of blindness in the African-American community. It affects 2 million Americans overall (Congdon et al., 2004; Lee et al., 2007). Current therapy revolves on lowering eye pressure using topical eyedrops. Patient understanding of and adherence to complex medical regimens is often poor (Balkrishnan, Bond, Byerly, Camacho, & Anderson, 2003), frequently resulting in the need for costly and high-risk surgical drainage procedures, including trabeculectomy and tube shunt procedures.

Various routes of administration may be used for intraocular drug delivery. These include oral and topical delivery and injections of various kinds: subconjunctival, sub-tenon, retrobulbar, intravitreal, and systemic (intravenous). Disease circumstances and the nature of the drug control the selection of route of administration. Less than 5% of topically administered pharmaceuticals reach the anterior chamber, making it almost impossible for them to reach the posterior segment. Even though the lacrimal turnover rate is only about 1 μl/min, the excess volume of the instilled fluid flows to the nasolacrimal duct rapidly in a few minutes (Urtti & Salminen, 1993). Systemic drug delivery, although it can deliver drugs to the posterior segment, but often is precluded by systemic side effects of doses required to overcome blood dilution and the blood–retinal barrier.

Current intraocular drug delivery devices include the Retisert, Vitrasert, Ozurdex, Medidur, and Neurotech's NT-501. All of these require intravitreal procedures and often suturing. These are single drug agents targeting chronic uveitis such as fluocinolide – Retisert and dexamethasone – Posurdex (Brumm & Nguyen, 2007), CMV retinitis such as ganciclovir – Vitrasert (Koch, Gumbel, Hattenbach, & Ohrloff, 1999), diabetic macular edema such as Medidur (Grover, Li, & Chong, 2008), and the dry form of macular degeneration such as ciliary neurotrophic factor-NT-501 (Sieving et al., 2006). None of these devices are refillable, nor do they target glaucoma or the wet (exudative) form of macular degeneration, which are the leading causes of severe visual loss. There have been a few attempts made towards refillable ocular drug delivery devices, but all of them require either active control or sutures and none of them have been

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implanted in the lens capsule (Lo et al., 2008; Yao, Yang, & Tai, 2002).

We propose a new approach that leverages the frequency of cataract extraction and the space within the lens capsule. Cataract procedures are the most common surgery (~3,000,000 in the US annually; indeed, clear lens extractions (technically the same procedure as a cataract extraction) are routinely performed simply to eliminate the need for glasses or contact lenses). Intraocular lenses placed at time of surgery leave considerable unfilled circumferential space in the lens capsule. The use of this untapped area is a novel approach for potential drug delivery (Fig. 1). The capsule drug ring (CDR) is a device designed to be implanted in the peripheral lens capsule during or after cataract surgery without sutures.

Avastin®, the drug of interest in this study has been thoroughly investigated as a potential alternative anti-angiogenic for treatment of AMD. A recent randomized control trial between Avastin and Lucentis (the anti-VEGF Fab fragment of Avastin) showed no difference in early efficacy in treatment of neovascular AMD (Subramanian et al., 2009). Intravitreal injection of bevacizumab (Avastin®) had resulted in a significant decrease in macular edema and improvement in visual acuity (Iturralde et al., 2006; Lang, 1995). Intravitreal injection of Avastin® for patients with macular edema due to non-ischemic central retinal vein occlusion (CRVO) resulted in a significant decrease in central retinal thickness (CRT) (Beutel et al., 2008). Intravitreal injections of bevacizumab versus triamcinolone acetonide were also compared in proliferative diabetic retinopathy showing that bevacizumab had the lowest levels of VEGF and potentially diminishes not only VEGF but also SDF-1alpha. These findings suggest that intravitreal bevacizumab may influence intraocular mediators beyond VEGF (Arimura et al., 2009).

The objectives of the present study were to develop a novel intraocular device that fits in the lens capsule and to determine the feasibility of developing a refillable reservoir for sustained drug release. Specifically, device characterization with respect to membrane type and pore size, valve bonding and functionality and in vitro testing of the drug release kinetics (PVA and Avastin® concentrations) were carried out to estimate the device feasibility.

2. Methods

2.1. Materials

Avastin® molecular weight approximately 149 kDa (Bevacizumab (Avastin®, Genentech, South San Francisco, CA)) is a recombinant humanized monoclonal immunoglobulin G1 antibody that inhibits human vascular endothelial growth factor (VEGF). It is approved by the United States Food and Drug Administration for intravenous use. Polyvinyl alcohol 87–89% hydrolyzed and mwt 146–186 kDa was purchased from Sigma–Aldrich.

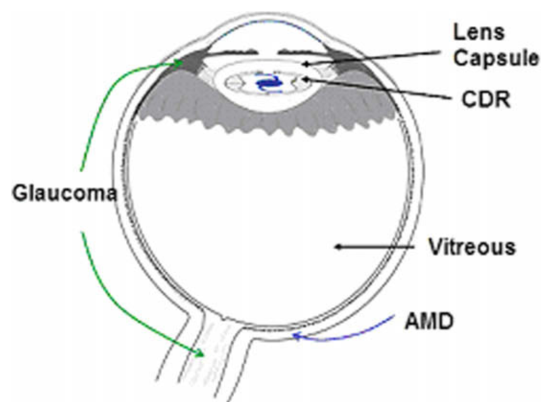

Fig. 1. The schematic diagram of eye showing CDR location inside lens capsule.

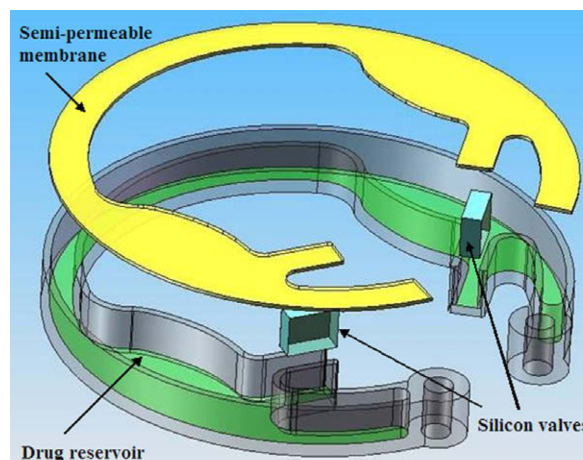

Fig. 2. The schematic diagram showing CDR architecture. The drug reservoir (shell), silicone valves and semi-permeable membrane are shown in the diagram.

2.2. CDR device fabrication

2.2.1. Assembly

The reservoir shell of the CDR was manufactured by milling poly methyl methacrylate (PMMA) sheet (Cat. number: ME 303011, Perspex, Goodfellow, Inc., PA) using a CNC machine with a tolerance of ±0.0005″ (~±12.5 μm). A ring of 13.0 mm outside diameter and 9.2 mm inside diameter was made from a Perspex sheet of 1.0 mm thickness. The wall thickness of the ring was 0.1 mm including the sidewalls and bottom wall. The volume of the drug reservoir was 50 μl. A 1 mm wide port is configured on the inner face of the shell to allow for easy access to the silicone valves (Part number: HT-6135, Bisco Silicones, IL). The valves are made from a sheet of 254 μm thick silicone by cutting thin strips of 1 mm × 3 mm using a knife plotter (Part number: FC5100-75, Graphtec, CA). The valves are attached to the inside edge of the CDR shell using an epoxy (Part number: Loctite 4011, Henkel Corporation, CT). The same epoxy was used to bond semi-permeable membrane (Part number: VSWP02500, Millipore, MA). The membrane was cut to appropriate ring size using a customized coring tool to obtain smooth edges.

2.2.2. Valve competency testing

Valve competency testing was performed via pressure monitoring. The PMMA shell reservoir's open face was closed by the semi-permeable membrane. A standard non-coring 27 G cannula was used to re-enact 12 refilling procedures by inserting the cannula 12 times through the valve. The PVA matrix was injected into the device using a 3 ml plastic syringe (BD, NJ). An in-line pressure transducer (Part number: 6069, Utah Medical Products, Inc., UT) was used to detect leakage which was defined as a reduction in pressure by 15%. The valve was then considered to be competent if no change in pressure greater than 15% was detected with this in-line pressure transducer.

2.3. Membrane permeability assay

The objective of this experiment was to assess the permeability of Avastin® (drug of interest) across various semi-permeable membranes in vitro. This information will help in choosing the semi-permeable membrane of suitable kinetics to be incorporated in the device for drug release studies. Experiments were carried out

in a well-stirred two-chamber side-by-side diffusion cell system with effective diffusion area around 0.8 cm^2. Experiments were carried out with Avastin®. The semi-permeable membranes were sandwiched between the two diffusion half-cells with the edge of the membrane sealed with parafilm. Cellulose ester (100 nm and 25 nm pore size) and polypropylene (100 nm) were the semi-permeable membranes used to construct the membrane systems in Table 2 in the present study. The membranes are 100 μm in thickness. The diffusion cell was placed in a circulating water bath at 36 ± 1 °C. Unless otherwise stated, 2 ml of balanced salt solution (BSS) and 2 ml donor solution were then pipetted into the receiver and donor chambers, respectively. The donor solution was prepared by mixing an appropriate amount of Avastin® in BSS, typically in the range of 30–100 μg/ml. Twenty-microliter aliquots were taken from the donor chamber, and 1 ml samples were withdrawn from the receiver chamber at predetermined time intervals (1–5 h depending on membrane). Fresh BSS solution was then added back to the receiver chamber to maintain a constant volume in the chamber.

For the purpose of the present study, the free aqueous diffusion coefficient (D) of Avastin® was determined under the assumption that Avastin® has similar frictional coefficient ratio as bovine serum albumin (BSA). The diffusion coefficient of BSA at 20 °C in pure water is 6.1×10^{-7} cm^2/s (Cantor & Shimmel, 1980). The free aqueous diffusion coefficient of Avastin® at 37 °C could be calculated using the diffusion coefficient of BSA and correcting for the molecular weight difference and the viscosity of water at 37 °C.

$$D_{\text{Avastin}} = D_{\text{BSA}} \frac{\eta_{20\,^{\circ}\text{C}}}{\eta_{37\,^{\circ}\text{C}}} \left(\frac{M_{\text{BSA}}}{M_{\text{Avasti}}} \right)^{1/3} \tag{1}$$

where $\eta_{20\,^{\circ}C}$ is the viscosity of water at 20 °C, $\eta_{37\,^{\circ}C}$ the viscosity of water at 37 °C, M_{BSA} the molecular weight of BSA, and $M_{Avastin}$ the molecular weight of Avastin®.

2.4. Drug release experiments

To assess diffusion from the CDR, Avastin® was lyophilized and reconstituted to a concentration of 2 or 4 mg of drug mixed with 50 or 75 mg/ml of polyvinyl alcohol (a stabilizing carrier) in 50 μl of total volume injected into the CDR. Each CDR was placed in a vial with 4 ml of BSS solution. The volume 4 ml was chosen to approximate the human vitreous volume. The CDRs used in this study were the same design as stated in the CDR device section but using 2 mm sheets of PMMA. We believe that the dissolution kinetics will not be altered by the thickness of the impermeable polypropylene sheets as long as the thickness and area of the semi-permeable membrane remains the same. The vials were placed on a heating pad at 40 °C. One milliliter samples were taken at predetermined time intervals (approximately 1 day). Fresh BSS was replaced to remain a constant volume in the vial.

2.5. ELISA for Avastin® quantification

Briefly, the 165-amino acid variant of human recombinant VEGF were immobilized on Microlite 2 (Thermo Labsystems, Franklin, MA). The samples to be assayed were diluted so as to be within the linear range of the assay. Samples and standard solutions were diluted in StabilCoat reagent (Surmodics, Inc., Eden Prairie, MN). The bound bevacizumab was detected with a goat antihuman IgG/Fc antibody labeled with (HRP) horseradish peroxidase (Jackson ImmunoResearch Lab., Inc., PA). The detection of HRP was performed with HRP substrate solution and 1 M H_2SO_4 for stopping the reaction. The wells were then transferred to a transparent 96 well plates for color absorbance measurement at 450 nm with correction at 562 nm.

2.6. Accelerated stability testing for (Avastin® + PVA)

At supraphysiological temperatures, drug degradation is accelerated, allowing us project product shelf life or compare relative stability of alternative formulations. The Arrhenius equation describes the relationship between storage temperature and degradation rate. Four vials of Avastin® (0.14 mg/ml) + PVA (50 mg/ml) were prepared. One vial placed in 4 °C was served as control. ELISA

Table 1
Summary of infusion pressures for silicone valves punctured with a 27 G needle (mean ± SE, N = 3).

Number of punctures		Infusion pressure (kPa)
Valve 1	Valve 2	
1	1	70.4 ± 1.6
12	1	67.73 ± 1.49
12	12	62.28 ± 1.59

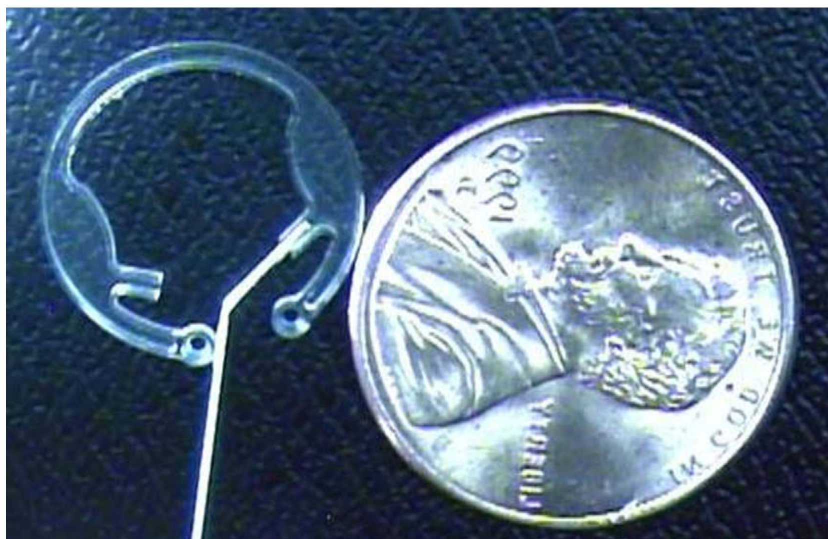

Fig. 3. The picture of a prototype prior to membrane and valve assembly with a 27 G cannula in the valve access port.

was performed for Avastin® activity. The other three vials were placed at 70 °C, 60 °C, and 50 °C. Assuming first order kinetics:

$$\ln K = \frac{-E_a}{RT} + \ln A \quad (2)$$

where K is the rate constant, E_a the activation energy, A the pre-exponential factor, T the temperature (K), R the gas constant.

Table 2
Permeability and diffusion coefficients of Avastin® across semi-permeable membranes in vitro (mean ± SE, $N = 3$).

Avastin® permeability coefficient	CE 100 nm	CE 25 nm	PP 100 nm
Permeability coefficient (10^{-7} cm/s)	1.74 ± 0.06	0.99 ± 0.10	11.80 ± 2.33

By plotting ln K versus $1/T$ one can predict the rate constant at 37 °C (body temperature).

3. Results

3.1. Fabrication

The CDR shell was fabricated at the U. Utah Department of Mechanical Engineering workshop facility. An example of such prototype (without overlaying membrane) with a 27 G cannula in the valve port is shown in Fig. 3. The CNC machining of the Perspex sheet allowed us tight control over the geometrical dimensions with less than 2% variability.

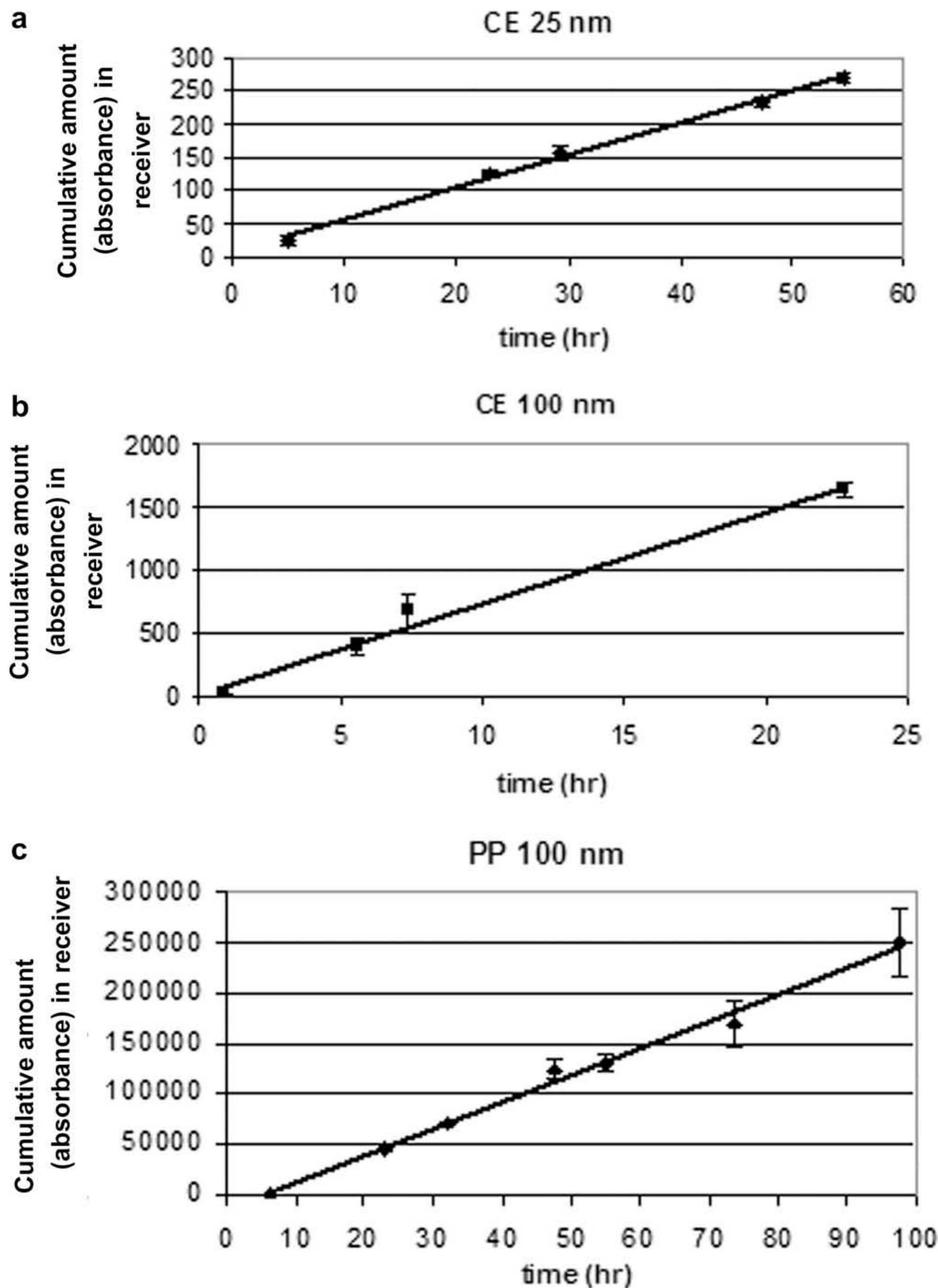

Fig. 4. Permeability plots for (a) CE 25 nm, (b) CE 100 nm, and (c) PP 100 nm, respectively.

3.2. Valve competency tests

One of the challenges with this "rigid" design of CDR was removal of trapped air as it could limit drug volume or induce excess pressure on the valve membrane and subsequent difficulties in refilling. To alleviate this problem, both membranes were prepunctured with a 27 G cannula to allow easy escape for the trapped air. The CDR prototypes were loaded with 50 mg/ml PVA solution with simultaneous recording of the infusion pressure using an in-line pressure transducer. The infusion pressure applied manually was increased until PVA leakage was observed. The same experiment was reported for multiple membrane punctures to ensure mechanical integrity of the valves over long durations of utility. The infusion pressures for 50 µl PVA injected are listed in the Table 1. In each of the experiments, no leakage was found from either valves or membrane interface after PVA injections. It should be noted that the infusion time required to completely fill the reservoir was less than 1 min.

3.3. Membrane permeability assay

Table 2 shows the permeability coefficient results for Avastin® across the semi-permeable membranes. The hydrophilic CE membrane was superior to the hydrophobic polypropylene (PP), likely due to the hydrophobic nature of PP that could interact with Avastin®. Fig. 4 shows the cumulative amount of Avastin® transported in the receiver versus time for the three different membranes tested. The PP membrane showed a lag time between 3 and 6 h ($n = 3$) with a high and undesirable permeability coefficient. The three sets of data were statistically significant with $p < 0.05$. The cellulose ester membrane of 100 nm provided a higher permeability coefficient (~2 times) than 25 nm as expected. These results suggest that the 25 nm CE will approximate near zero-order kinetics. The free aqueous diffusion coefficient of Avastin® was estimated to be 6.6×10^{-7} cm^2/s using the diffusion coefficient of BSA, viscosity of water at 20 °C and 37 °C, and Avastin® and BSA molecular weights (see Eq. (1)). The diffusion coefficients for thickness of 100 µm for each PP 100 nm, CE 100 nm and CE 25 nm are 1.18×10^{-8}, 1.74×10^{-9}, and 0.99×10^{-9} cm^2/s, respectively.

3.4. Drug release experiments

Different Avastin® and PVA concentrations were tested in the CDR for dissolution rates. Fig. 4 represents cumulative amount of Avastin® in micrograms in the 50 mg/ml PVA solution. Both 75 and 50 mg/ml PVA were tested, however the 50 mg/ml concentration was easier to handle and inject into the CDRs. As shown in Fig. 5, linear delivery curve (approaching zero-order kinetics) was achieved after 2 days with estimated rate of diffusion of 0.06–0.08 mg/day (which is less than the standard monthly dose of Avastin® of 2.5 mg/month but still in effective range).

3.5. Accelerated stability testing for (Avastin® + PVA)

The accelerated stability testing in our study depends mainly on change of activity of Avastin® and not any physical changes. According to our preliminary data in Fig. 6, the reaction rate (K) at 37 °C was found to be 0.00166 day^{-1}. Further experiments are required at more temperature points and to compare the Avastin® + PVA formula with Avastin® only.

4. Discussion

A circular prototype of the capsule drug ring was developed to maximize the volume available in the capsular bag with a reservoir volume of approximately 50 µl. This device is a novel idea for treatment of anterior and posterior chronic eye diseases. It is the first to use the capsular bag as a medium for drug delivery. The CDR reported here consists of (i) drug reservoir shell; (ii) semi-permeable hydrophilic membrane for continuous and controlled drug elution; and (iii) two silicone membrane check valves for refills as shown in Fig. 2. Polyvinyl alcohol (PVA) was used as the polymer carrier to enhance controlled release and stability of the drug, Avastin®. We successfully demonstrated feasibility of fabrication, structural integrity and bonding of the semi-permeable membrane to the shell, valve competency, near zero-order kinetics of release, and drug stability within a polymer matrix.

Multiple valves are provided to permit multiple drug chambers to ensure versatility of the device for multiple ocular diseases. The CDR shell has two eyelets at the open ends to allow for rotation and manipulation in the lens capsule after implantation. Based on the needs of the eye disease, the semi-permeable membrane of the CDR could be faced either to the anterior chamber or to the posterior chamber for drug delivery. These two properties (multiple drug chambers and diffusion side facing either the anterior or posterior chamber) serve as a platform for many chronic diseases that need multiple drugs.

The incorporation of valves in the CDR was successful ensuring the potential for refillability. Semi-permeable membranes were also successfully bonded to the PMMA shell. The comparison between the diffusion coefficients across semi-permeable membranes or in free aqueous solution shows the importance of the semi-permeable membrane for sustained drug delivery system for the CDR device. These findings need to be confirmed for obtaining near zero-order kinetics up to 6 months.

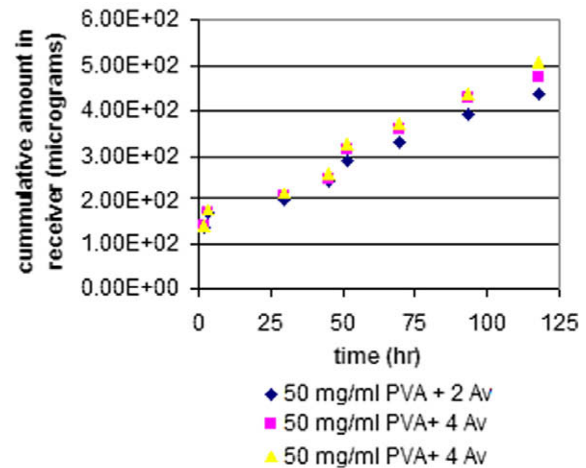

Fig. 5. Cumulative Avastin® amount released versus time.

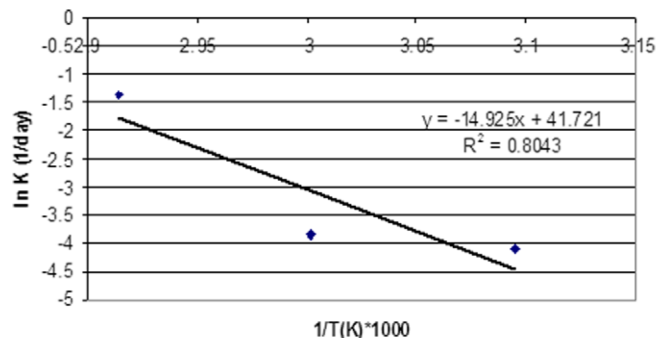

Fig. 6. Arrhenius plot. The log k values derived in this study are plotted versus inverse temperature (K).

A number of additives such as urea, amino acids (in particular glycine and arginine) and poly alcohols have been demonstrated to reduce the rate of protein aggregation (Baynes & Trout, 2004; Cleland, Powell, & Shire, 1993). The presence of PVA acts both as a stabilizer and an increasing viscosity agent for Avastin® in the CDR.

In summary, a novel non-biodegradable drug delivery device specifically designed to be implanted in lens capsule has been developed, fabricated and tested successfully to determine adequate drug formulation with PVA carrier for near-zero order elution. Further experiments will entail implantation of the CDR in a rabbit model (new to assess any future potential problems in humans). Long term implantation may result in the occlusion of pores if significant fibrosis occurs. In addition, ocular zonular integrity will be studied and monitored; however our target is to have total mass <200 mg as human cataracts typically are 200–250 mg in mass, which is tolerated by normal zonules. Toxicity and biocompatibility will be investigated, in addition to the pharmacokinetics profile of Avastin® in vivo.

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References

Arimura, N., Otsuka, H., Yamakiri, K., Sonoda, Y., Nakao, S., Noda, Y., et al. (2009). Vitreous mediators after intravitreal bevacizumab or triamcinolone acetonide in eyes with proliferative diabetic retinopathy. *Ophthalmology, 116*(5), 921–926.

Balkrishnan, R., Bond, J. B., Byerly, W. G., Camacho, F. T., & Anderson, R. T. (2003). Medication-related predictors of health-related quality of life in glaucoma patients enrolled in a medicare health maintenance organization. *The American Journal of Geriatric Pharmacotherapy, 1*(2), 75–81.

Baynes, B. M., & Trout, B. L. (2004). Rational design of solution additives for the prevention of protein aggregation. *Biophysical Journal, 87*(3), 1631–1639.

Beutel, J., Ziemssen, F., Luke, M., Partsch, M., Bartz-Schmidt, K. U., & Gelisken, F. (2008). Intravitreal bevacizumab treatment of macular edema in central retinal vein occlusion: One-year results. *International Ophthalmology*.

Brumm, M. V., & Nguyen, Q. D. (2007). Fluocinolone acetonide intravitreal sustained release device—A new addition to the armamentarium of uveitic management. *International Journal of Nanomedicine, 2*(1), 55–64.

Cantor, C. R., & Shimmel, P. R. (1980). *Biophysical chemistry: Part II: Techniques for the study of biological structure and function*. W.H. Freeman.

Cleland, J. L., Powell, M. F., & Shire, S. J. (1993). The development of stable protein formulations: A close look at protein aggregation, deamidation, and oxidation. *Critical Reviews in Therapeutic Drug Carrier Systems, 10*, 307–377.

Congdon, N., O'Colmain, B., Klaver, C. C., Klein, R., Munoz, B., Friedman, D. S., Kempen, J., Taylor, H. R., & Mitchell, P. (2004). Causes and prevalence of visual impairment among adults in the United States. *Archives of Ophthalmology, 122*(4), 477–485.

Geroski, D. H., & Edelhauser, H. F. (2000). Drug delivery for posterior segment eye disease. *Investigative Ophthalmology & Visual Science, 41*(5), 961–964.

Grover, D., Li, T. J., & Chong, C. C. (2008). Intravitreal steroids for macular edema in diabetes. *Cochrane Database of Systematic Reviews* (1), CD005656.

Iturralde, D., Spaide, R. F., Meyerle, C. B., Klancnik, J. M., Yannuzzi, L. A., Fisher, Y. L., Sorenson, J., Slakter, J. S., Freund, K. B., Cooney, M., & Fine, H. F. (2006). Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: A short-term study. *Retina, 26*(3), 279–284.

Koch, F. H., Gumbel, H. O., Hattenbach, L. O., & Ohrloff, C. (1999). Intravitreal endoscopic visualization of intraocular ganciclovir devices: Improved long-term treatment of CMV retinitis. *Klinische Monatsblatter Fur Augenheilkunde, 214*(2), 107–111.

Lang, J. C. (1995). Ocular drug delivery: Conventional ocular formulations. *Advanced Drug Delivery Reviews, 16*, 39–43.

Lee, P. P., Levin, L. A., Walt, J. G., Chiang, T., Katz, L. M., Dolgitser, M., Doyle, J. J., & Stern, L. S. (2007). Cost of patients with primary open-angle glaucoma: A retrospective study of commercial insurance claims data. *Ophthalmology, 114*(7), 1241–1247.

Lo, R., Li, P. Y., Saati, S., Agrawal, R., Humayun, M. S., & Meng, E. (2008). A refillable microfabricated drug delivery device for treatment of ocular diseases. *Lab on a Chip, 8*(7), 1027–1030.

Sieving, P. A., Caruso, R. C., Tao, W., Coleman, H. R., Thompson, D. J., Fullmer, K. R., & Bush, R. A. (2006). Ciliary neurotrophic factor (CNTF) for human retinal degeneration: Phase I trial of CNTF delivered by encapsulated cell intraocular implants. *Proceedings of the National Academy of Sciences of the United States of America, 103*(10), 3896–3901.

Subramanian, M. L., Ness, L., Abedi, G., Ahmed, E., Daly, M., Feinberg, E., Bhatia, S., Patel, P., Nguyen, M., & Houranieh, A. (2009). Bevacizumab vs Ranibizumab for age-macular degeneration: Early results of a prospective double-masked, randomized clinical trial. *American Journal of Ophthalmology, 9*, 9.

Urtti, A., & Salminen, L. (1993). Minimizing systemic absorption of topically administered ophthalmic drugs. *Survey of Ophthalmology, 37*(6), 435–456.

Yao, T. J., Yang, X., & Tai, Y. C. (2002). *Sensors and Actuators A, 97*, 771–775.