Responsive Hydrogels based lens structure with configurable focal length for Intraocular Lens (IOLs) application

*Yifan Li[1], Ding Wang[1], Jack Richardson[1], Ben Bin Xu[1]**

[1]Smart Materials and Surfaces Lab, Faculty of Engineering and Environment, Northumbria University, Newcastle upon Tyne, UK, NE1 8ST
Corresponding author email: ben.xu@northumbria.ac.uk

Summary: Stimuli-responsive hydrogel has attracted widespread interests in bio-applications, especially in bio-optical systems that need tuning and adjustment of their optical performance. In this paper, we have investigated the materials and structural designs for the potential intraocular Lens (IOLs) design by studying swelling induced morphology changes and subsequently optical properties of ionic responsive Poly (Acrylamide-*co*-sodium acrylate) hydrogel. The equilibrium swelling ratio and swelling kinetics of gel were measured under both free standing and confined conditions. The Poly (Acrylamide-*co*-sodium acrylate) hydrogel has shown reversible swelling response to the ion concentration. Autonomous focusing of the gel lens was demonstrated under the certain ionic stimulus. Initial optical results have been presented with designable stimuli-responsive focal length shifting under structural confinement.

Keywords: Hydrogel, stimuli-responsive, intraocular Lens, ionic.

Introduction

One of the recent research interests in intraocular lens (IOLs) technology is to achieve variable focal lengths by using suitable materials and novel designs. The most common solution is to either directly fabricate the lens and its components onto curved surfaces by moulding, or geometrically reshape a planar system [1-4]. By far, all reported IOLs designs are of fixed focal length, the technical challenge remains to be addressed under the term of developing gel lens with adjustable focal length in an autonomous and reversible manner. From the perspective of customer experiences, the IOLs with self-regulating focal length could offer convenient care solutions to perspective patients by providing vision tolerance to avoid over-sight or/and over-intensity after surgery [2].

By applying various external stimuli such as temperature, pH, electric and magnetic fields, and chemical triggers, hydrogel can undergo reversible deformation to change its size and shape [4-11]. Stimuli-responsive hydrogels have been developed into various sensor and actuator applications include bio-medical sensors, artificial muscle actuators, scaffolds for tissue engineering, active surfaces and drug delivery systems [12-15]. The swelling and de-swelling of the polymer network was firstly discovered as a result from reversible titration of weakly ionised polyelectrolyte gels [3]. Given a proper boundary condition, curvilinear layouts could be generated on the surface of gel during swelling. Such stimuli induced geometrical change will result in strong nonplanar imaging capability and autonomous control [16-18]. Recent study by Dong and co-workers [19] presented a hydrogel based adaptive liquid lens, where the water-oil interfaces were pinned and deformed by actuating ring-shaped hydrogel structures by changing temperature and pH, mimicking the mechanism of a human eye. The utilisation of responsive materials could simplify the lens design without degrading the field of view, focal area, illumination uniformity, or image quality [20].

In this article, we introduce a conceptual design to confine the circular gel structure on the rim with a 3D printed holder. The purpose is to configure the curvature of gel lens in a coordinated manner under the ionic stimulus, to achieve variable focal length autonomously. When swelling occurs under the given confinement, the original thickness of fabricated curved lens changes in an elastic and reversible way that allow us to control the curvature of the lens. This actuation is defined precisely by the nature of the polyelectrolyte gel in this work and the kinetic is studied. The investigation of the focal length change suggests that the fabricated gel lens covers the whole range of the human eyes. The conceptual gel lens in this study could be an active substrate to integrate with other elements for advanced eye prosthetic device development.

Results and discussion

The gel lens structure was designed to be confined by a 3D printed holder with hollowed structure for the swelling tests (Figure 1a-1d). Stimuli responsive poly(acrylamide-*co*-sodium acrylate) (PAAM-*co*-NaAc) hydrogels (Figure 1e) has been used. As the copolymer gel can response to both ionic and thermal stimuli [21], the degree of swelling and morphology change of the thin gel layer under certain confinement can be varied through changes to either the ionic strength of the phosphate buffered saline (PBS) solution (ionic strength= 150 mM) or temperature. The conceptual gel lens design has used a circular shape with a diameter of 13.8 mm, and varied thicknesses. The prototyping of gel lens consisted of three steps (Figure 1f). Firstly, the self–designed micro-mould was assembled. Secondly, the reaction-moulding of the gel was performed. And finally, the cover slip was removed to release the lens. The lens was designed with different aspect ratios by controlling the initial height from 250 μm to 2 mm, with a fixed projection diameter of 13.8 mm.

The gel swelling test was performed in PBS solutions at room temperature (20 ^{o}C) with three different confining conditions, free standing (bulk, Figure 2a), side confinement (Figure 2b), and rim confinement (Figure 2c). As illustrated in Figure 2d, the conceptual lens design with rim confinement could present a focal length change when the nonlinear morphology changes occur as a result of the ionic swelling. The swelling results are compared in Figure 2e, the rim confinement swelling presents the significant deformation with a H/h ~ 2.42, while the free standing swelling achieve the equilibrium at a H/h ~ 1.56 for one dimension, and a H/h ~ 2.06 for side confinement. Under the rim confinement, the lens structure could achieve higher deformation from the central axial, yielding a significant curvature changes during the swelling process.

The next step was to build a multi-point laser marking based focal length measurement system (Figure 3a) to characterize the focal length changes for the gel based lens structure under ionic swelling. By setting the dimensional variables of the system and controlling the position of the laser input, we will receive the laser mark in the paper receiver. As shown in Figure 3b, the distance from lens to paper receiver can be set by controlling the Z-stage, where I_c is the position when the laser gets through the centroid of the gel lens and the I_e is the laser gets through the edge, we will have focal length ~ $Dl/(D-d)$. For each measurement, one I_c and at least three I_e need to be measured. Resulted sample marks of the I_c and I_e are shown in Figure 3c-3d. As a dynamical process, we used the ionic strength in buffer solution to control the swell ratio (H/h), the calculated focal lengths are shown in Figure 3e. When the swelling started, the focal length was start drop into measurable range at ~ 26 mm, then keep dropping when the lens was further swollen. The focal length reached a practical range of ~ 15 when the H/h is 1.7, and remained relatively stable within this range. We noted a wide distribution of the data during the high swelling state, this was caused by the data processing when the Numerical Aperture (NA) was applied to compensate the deflection, while the actual incident angle was hard to capture during the dynamic swelling. The experimental set will be further improved with laser confocal system to identify the laser incident angle. In all, the responsive gel based lens supported by the rim confinement have demonstrated variable-focus ability and can autonomously respond to ionic stimuli.

This responsive hydrogel-based lens is easy to fabricate and its stimuli-responsive nature offers a highly adaptable property, which could be used as substrate to be integrated with other elements such as circuits and sensor for prosthetic application. Moreover, the mechanical confinement has realised a wide range of focal length change, which could significantly improve the vision quality by achieving a wide fields of view. However, there are still some work need be done to understand the mechanics of the geometrical curvature change under rim confinement, and the calculation correction of focal length changes at high swelling level.

Conclusion

We have developed a novel IOLs technique with ionic responsive gel under specific confinement. The ionic swelling induced morphological transformation enabled a wide range of focal length changes ($\infty \rightarrow$ 10 mm). This technology also enables simple and cost effective fabrication as well as reasonable fast response times (in the a few minutes). The responsive gel based lens has a highly adaptive property and could autonomously respond to changes of ionic strength in the environment and provide visible output signals. It could also be used as substrate to integrated other elements to generate novel opto-electronic systems for prosthetic applications.

Experimental

3D printing micro mold and device assembly: The lens mold was printed via Objet 24 desktop system with photo cured acrylic based material. The mold design employed standard contact lens parameters, and was completed in Solidwork software before being loaded into a Strasys® Objet24 system for printing. The printed parts were cleaned and rinsed with isopropanol (IPA), before being annealed on a hot plate at 100 ^{o}C for 15 min. The assembly of gelation chamber was constructed by the printed mold and a glass cover slip.

Gelation and lens fabrication: The Poly (Acrylamide-*co*-sodium acrylate) hydrogel was synthesized with 825 mM acrylamide, 115 mM sodium acrylate, 4.5 mM *N*,*N*'-methylenebis(acrylamide), 5 mM of Flourescein *o*-acrylate (for swelling test only), 0.3 μL of *N*,*N*,*N*',*N*'-tetramethylethylenediamine and 1.0 μL of a 10 wt% aqueous ammonium persulfate solution. Gelation was completed within 20 min in the assembled chamber. After removing the coverslip, the gel lens can be obtained and then put into a phosphate buffer saline solution (Sigma-Aldrich) prepared with a total ionic strength of 150 mM.

Gel swelling study and focal length measurement with laser marking: The swelling testing was carried out via direct optical observation of the fluorescence dyed gel products. For the free standing mode, the gel was cut into cube shape with varied original dimensions of 2.5mm, 5mm and 7.5mm. For the side confined and rim confinement swelling tests, the gel sheets used the same diameter of 13.8 mm, and the sheets with varied thickness of 250 μm, 500 μm and 750 μm respectively. The lens sheet has a thickness gradient similar with spherical cap. Gels were allowed to equilibrate for 2 h in the PBS solution with certain ionic strength and the gel was imaged using either a Zeiss® Axiovert 200 inverted optical microscope (2.5x, 5x and 10x objectives) or a Zeiss® LSM 510 META laser scanning confocal fluorescence microscope, where a HeNe laser (wavelength 520 nm) was used to excite the fluorescence fluorophore (detection filter: 480 nm). The focal length characterization was carried *via* a multi points laser marking and calculated the focal length. The low energy HeNe laser (power ~4mW, wavelength ~633 nm) was adopted in this measurement to prevent any possible degradations of the gel. The final focal length calculation was correct with the Numerical Aperture (NA), to compensate the deflection between then liquid/air interface.

Acknowledgements

The work was supported by the Engineering and Physical Sciences Research Council (EPSRC) grant EP/N007921/1 and Royal Society Research Grant-RG150662. The authors also acknowledge fundings from the EU-COST MP1106 network, Royal society of Chemistry and British Council.

References

[1] O. Findl, W. Buehl, R. Menapace, S. Sacu, M. Georgopoulos, G. Rainer, *Ophthalmology*, **2005**, *112*, p. 2004.
[2] M.A. Farbowitz, N.A. Zabriskie, A.S. Crandall, R.J. Olson, K.M. Miller, *J. Cataract. Refract. Surg.*, **2000**, *26*, 1339.
[3] R. Chiarelli, and D. De Rossi, in: *"Ionic Interactions in Natural and Synthetic Macromolecules*", A. Ciferri, A. Perico, Eds. Wiley, **2012**, pp. 581-620
[4] D. Schmaljohann, *Adv. Drug Deliv. Rev.*, **2006**, *58*, 1655.
[5] B. Xu and R. C. Hayward, *Adv. Mater.*, **2013**, *25*, 5555.
[6] B. Xu, Q. H. Liu, Z. G. Suo and R. C. Hayward, *Adv.Func. Mater.*, **2016**, *26*, 3218.
[7] G. Grassi, R. Farra, P. Caliceti, G. Guarnieri, S. Salmaso, M. Carenza and M. Grassi, *Am. J. Drug Deliv.*, **2005**, *3*, 239.
[8] K. Sawahata, M. Hara, H. Yasunaga and Y. Osada, *J. Controlled Release*, **1990**, *14*, 253.

[9] R. Yoshida, K. Sakai, T. Okano and Y. Sakurai, *Adv. Drug Deliv. Rev.*, **1993**, *11*, 85.
[10] J. Dolbow, E. Fried and H. D. Jia, *J. Mech. Phys. Solids*, **2004**, *52*, 51.
[11] H.L. Lim, Y. Hwang, M. Kar and S. Varghese, *Biomater. Sci.,* **2014**, *2*, 603.
[12] A. Richter, G. Paschew, S. Klatt, J. Lienig, K. Arndt and H.P. Adler, *Sensors* **2008**, *8*, 561.
[13] Y. Qiu, K. Park, *Advanced Drug Delivery Reviews*, **2012,** *64*, 49.
[14] I.M. El-Sherbiny and M.H. Yacoub. *Global Cardiology Science and Practice,* **2013**, *3*, 38.
[15] S.H. Lee, T.H. Kim, M.D. Lima, r.H. Baughman, S.J. Kim, *Nanoscale*, **2016**, *8*, 3248.
[16] R. Dinyari, S.B. Rim, K. Huang, P. B. Catrysse and P. Peumans, *Appl. Phys. Lett.,* **2008**, *92*, 091114.
[17] P. J. Hung, K. Jeong, G.L. Liu and L.P. Lee, *Appl. Phys. Lett.*, **2003**, *85,* 6051.
[18] S.B. Rim, P.B. Catrysse, R. Dinyari, K. Huang, and P. Peumans, *Opt. Express*, **2008**, *16*, 4965–4971).
[19] L. Dong, A.K. Agarwal, D.J. Beebe, and H.R. Jiang, *Nature*, **2006**, *442*, 551.
[20] H.C. Ko, M.P. Stoykovich, J. Song, V. Malyarchuk, W.M. Choi, C.J. Yu, J.B. 3rd Geddes, J. Xiao, S. Wang, Y. Huang, J.A. Rogers, *Nature*, **2008**, *454*, 748.
[21] V. Trujillo, J. Kim and R.C. Hayward, *Soft Matter*, **2008**, *4*, 564.

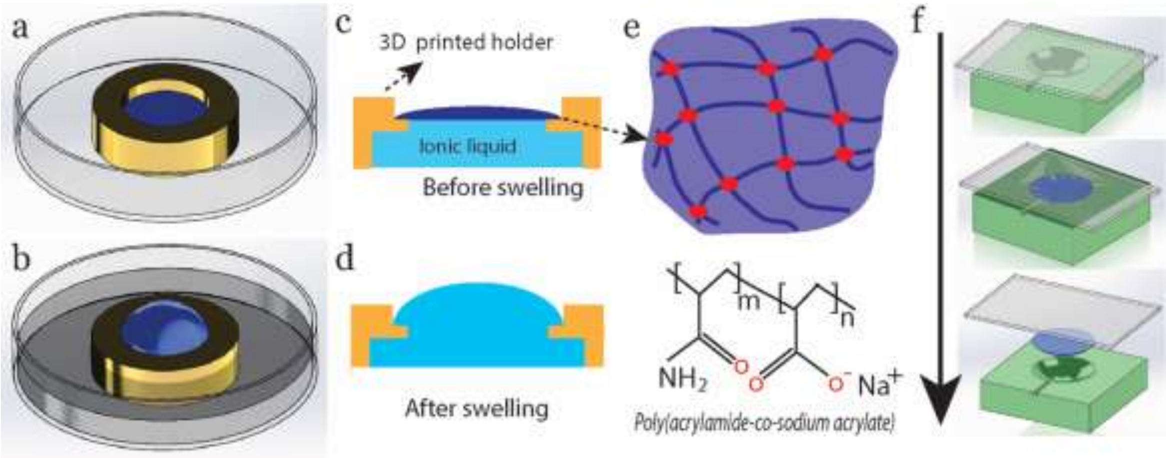

Figure 1. Experimental design of an ion-concentration controlled swelling hydrogel adaptive lens. The stimuli hydrogel is placed on a 3D printed holder to give a ring confinement during the swelling. (a) The pre-swelling set, (b) the Lens effect after swelling. The cross section views of pre-swelling state (c), and post swelling state (d). (e) The illustration of gel network and chemical composition for the PAAm-*co*-NaAc in our study. (f) from top to bottom, the gelation process in a micro-mould consisting of a 3D printed mould and a cover slip.

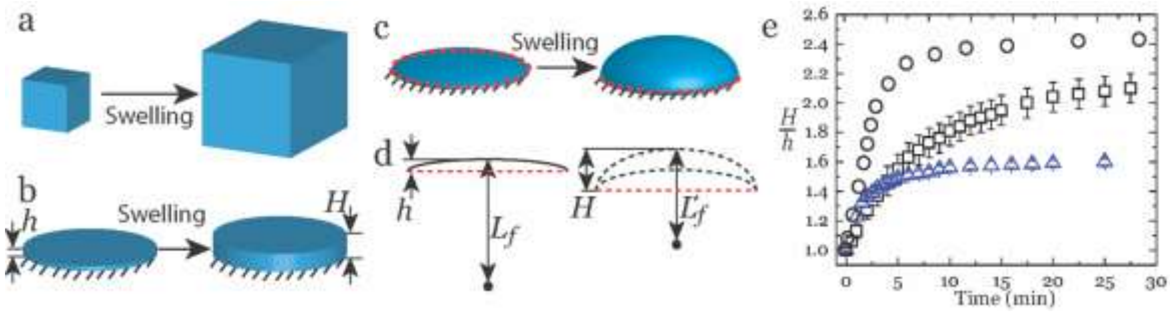

Figure 2. Schematic and measurement of the morphology change under different swelling state, (a) free standing, (b) one side confinement, (c) ring confinement for PAAm-*co*-NaAc gel lens, (d) the parameters to describe the morphology change of the lens, the original height *h*, the original Focal Length L_f, the height after swelling *H*, and the Focal Length after swelling L'_f. (e) The swelling kinetics of the gel under different confining state, free standing (Δ), side confinement (□), and ring confinement in this study (O).

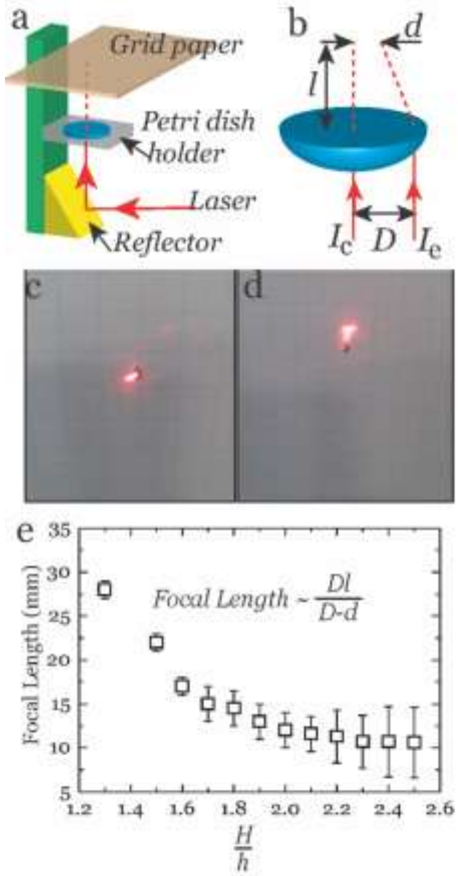

Figure 3. (a) The experimental set to determine the focal length for the lens during the ionic swelling by laser marking. (b) Dimensional parameters for calculation of the focal length. Sample laser targeting for (c)I_c and (d)I_e. (e) Calculated focal lengh with different swelling ratio for the PAAm-*co*-NaAc gel lens.