Delivering *in situ*-gelling hydrogels for ophthalmic drug therapies using a microinjection device

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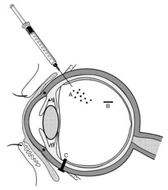
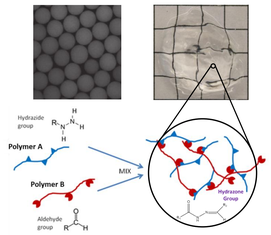
Introduction

The primary causes of vision loss in developed nations are related to diseases of the posterior eye (AMD, diabetic retinopathy, posterior uveitis, retinitis due to glaucoma, etc.).[1,2] However, this is a particularly difficult target tissue due to anatomic and physiologic limitations, resulting in few intravitreal treatment options being available. Intravitreal injections have been the preferred option, as they are facile, direct method of delivering therapeutic or delivery systems.

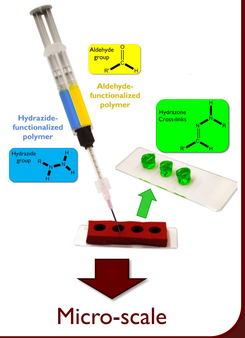


Source: Thrimawithana et al. (2011)[4]



However, in order to maintain therapeutic levels frequent injections may be required which greatly increases the risk of complications over time and is inconvenient and uncomfortable for the patient. We have developed injectable, degradable hydrogel-based materials for ophthalmic applications that could prolong drug release and have highly adjustable properties (swelling, refractive index, gelation time, and API uptake/release).

These materials have also shown promising *in vitro* results in many cases, but assessing their *in vivo* characteristics is difficult which require injections in the range of 1 – 5 µL (and up to 10 µL for humans). The hydrogel materials are traditionally prepared with a double-barrel syringe, and which has no volume control for this size range. Furthermore, single component µL-scale syringes cannot be used because these materials react and gel much too quickly for such devices. In fact, there are no devices that can effectively mix and precisely inject small volumes of two reactive polymer solutions. This project involves the development of a microinjector for two reactive polymer solutions that could be useful for ophthalmic applications.



Design Goals

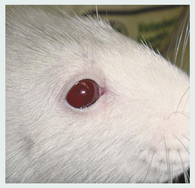
From our perspective

- Effectively mixes the two precursor polymers upon injection
- Controllably and precisely injects volumes in the 1–10 µL range through a narrow needle suitable for ophthalmic injections (> 30G)
- Injects these materials while preventing gelation and blockage within the needle
- Inexpensive → One time use

From the surgeon's perspective

- Device should be ergonomical
- Doesn't need to be operated too quickly
  - Surgery times can vary from 1-5 minutes
- Operation should be as similar as possible to the current process

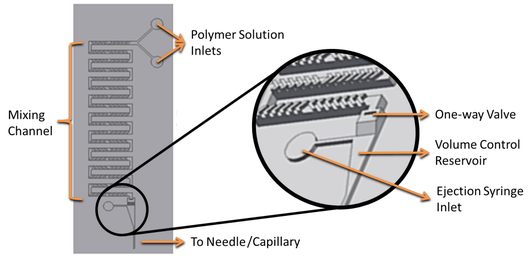
Current vitreal injections



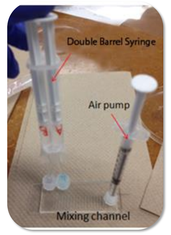
- Inject into a hole in the sclera made with a 30G needle
  - Blunt 33G needle and 10 µL syringe
- Two person operation
  - One to hold the needle in place
  - One to push the syringe plunger
- The time to place the needle through the hole may vary greatly (in minutes)

Results

The design



- Two separate inlets connect to a mixing channel with herringbone grooves[3] to promote mixing
- The mixing channel leads to a volume control reservoir with a one-way valve
- Another inlet in the volume control region allows for the material in the volume control region to be pushed through the outlet capillary
- Design retains two-person operation
  - One person to hold device, one person to operate syringes (which can be positioned further away from device)

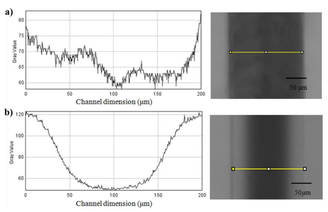


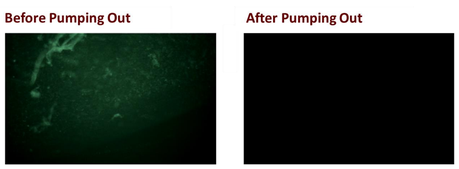
Device manufacture

- Each device is made of PDMS
  - Fabricated from a single mould before bonding to glass
  - Outlet silicon capillary is attached after bonding
- Moulds are fabricated using a 3D printer
  - Facile, rapid design modification
  - Precise control volume dimensions (0.5 – 1000 µl)

Mixing/ejection studies

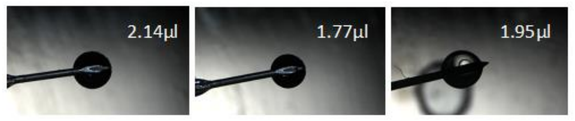
- Mixing studies performed with initial prototype
- Polymer solution mixing greatly enhanced by herringbone grooves
  - Near-complete mixing 17.5 mm in
- FITC-labelled polymers ejected by 10 mM PBS buffer
- 2 µL hydrogel droplets were pumped out with no polymer residues left in the reservoir
  - Laminar flow prevents material mixing





Volume control

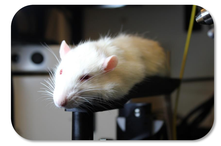
- Volume control was assessed by injecting hydrogel droplets into paraffin
  - Relatively spherical droplets formed, analyzed with ImageJ
  - 5.2 µL control volume ejects 4.3 ± 0.8 µL
- Successfully injected a range of different hydrogel combinations
  - A wide variety of gelation times (30 seconds – 5 minutes)
- Injected hydrogel materials into paraffin oil, onto glass surfaces, and into solutions of bovine vitreous humour at 37°C

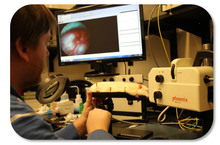


Results

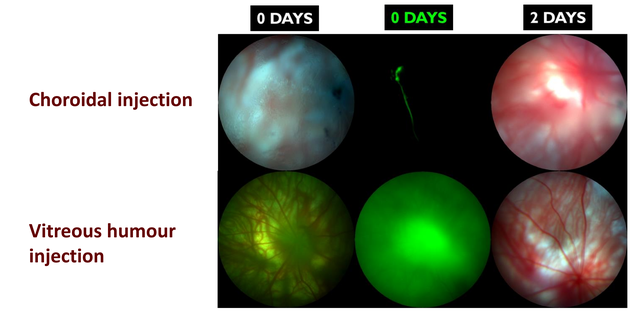
In vivo studies

- Injected long-chain, protein repellent, fluorescently-labelled poly(oligoethylene glycol methacrylate) POEGMA hydrogels into the vitreous humour of anaesthetized rats
- Getting the timing of the process is essential
  - Anaesthetizing (making sure that the rat doesn't wake up/blink during process)
  - Forming a visible hole in the sclera (via pre-coating the needle in Nile Blue A)
  - Priming the injector
  - Putting the capillary of the injector through the pre-fabricated hole and injecting





- Successfully injected ~5-10 µL of 11.25 wt% fluorescent POEGMA hydrogels into 5 rats
  - 4 in the vitreous humour, 1 in the choroid (tissue in between the sclera and the retina)
  - In the choroid case, hydrogel formed within the needle track
  - No increase in intraocular pressure observed and the rats retained their sight
- No fluorescence observed after 2 days
  - Gel may have not formed, was rapidly degraded, or the fluorescent tag was photo-bleached → albino rats
- Prior to histology (2 weeks post-injection), small, opaque gel-like materials were observed in the injected eyes (and not in the controls)
- Initial histology shows that injected eyes appear similar to controls



Conclusions/Future work

Progress thus far

- Designed a device to inject *in situ* crosslinking hydrogels in the eye in controlled volumes <10 µL for *in vivo* experiments
- The device is able to mix the two reactive polymers evenly and inject a controlled volume from blunt capillaries (33G equivalent) *in vivo*
- First time *in situ* reactively-crosslinking hydrogels injected into animal eyes *in vivo*

Future work

- Complete histology to confirm existence and biocompatibility of these hydrogels in the eye
- Perform further injections in non-albino rats to see if fluorescence can be maintained
- Attempt to show fluorescent drug release from these injected hydrogels *in vivo*

Acknowledgements and References

1. Myles, M. E.; Neumann, D. M.; Hill, J. M. *Advanced Drug Delivery Reviews* 2005, *57*, 2063–79.
2. Sheardown, H. *Future Medicinal Chemistry* 2012, *4*, 2123–2125.
3. Stroock, A.D. et al. *Science* 2002, *295*, 647-650.

NSERC CRSNG | Canada Research Chairs | J.P. Bickell Foundation | 20/20 NSERC Ophthalmic Materials Network | Vanier Canada Graduate Scholarships

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