

# Hydrogels in ophthalmic drug delivery system - A mini review

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## ABSTRACT

The frequent demand for effective eye therapies is acting as driving force for the development of injectable hydrogels as new medical devices for controlled delivery and filling purposes. The delicate structure and the protective physiological process of our eye exert a defense system against ophthalmic delivery of drug, which ultimately led to poor precorneal drug loss, resulting in poor ocular bioavailability. To improve ophthalmic preparation's bioavailability, there are valuable efforts directed toward newer drug delivery systems for ophthalmic administration. As we know that other conventional delivery system gives poor therapeutic response and bioavailability because tears have high fluid turnover and dynamics due to which rapid elimination of drug from the eye takes place. *In situ* polymeric formulations are drug delivery systems that are in sol form before administration in the body, but on administration, they undergo gelation *in situ*, to form a gel. The formation of gels depends on factors such as temperature modulation, pH change, presence of ions, and ultraviolet irradiation, from which the drug gets released in a sustained and controlled manner. This article introduces the properties and mechanisms of injectable hydrogels and summarizes their versatile application in the treatment of ophthalmic diseases, including age-related macular degeneration, cataracts, diabetic retinopathy, glaucoma, and intraocular cancers.

**Key words:** *In situ* polymeric formulation, cataract, diabetic retinopathy, glaucoma, intraocular cancer.

## INTRODUCTION

The human eye has a sophisticated multisegmented structure, and malfunction of any segment may cause permanent vision loss or may cause blindness. Eye segment is vulnerable to either inherited or contracted disorders [Figure 1]. The most commonly encountered diseases that cause visual impairment are cataract, glaucoma, diabetic retinopathy (DR), age-related disease, inflammation, and intraocular tumors. The physiology, biochemistry, and anatomy of the eye make this organ extremely impermeable to foreign substances. A major disadvantage of conventional ocular drug delivery system is that optimal concentration of drug would not reach in the required site of action. To treat eye disorders, the choice of administration of drugs is through topical instillation through eye drops.<sup>[1-3]</sup>

To date, only a limited number of technologies have been available for ophthalmic disorders and disease therapy. Surgery-based techniques are used as the major therapies for damaged tissue and the delivery of therapeutic components (i.e., drugs, protein/peptides, genes, and nanoparticles).<sup>[1]</sup> Surgical methods, however, are limited to therapies such as removal of the vitreous humor, refraction correction, glaucoma treatment, and corneal transplant. Although therapeutic molecules have played a critical role in the therapy of congenital and acquired diseases, the challenge remains to improve the efficacy of drug delivery and minimize side effects and the off-target rate.<sup>[4,5]</sup>

Commonly used eye drop have little permeability to the cornea and are thus limited to treatment in the outer segment of the

eye. In conventional administration approaches such as topical eye drops, subconjunctival injection, and intravitreal injection, several physiologic and biologic barriers exist that the therapeutic payload must overcome. These include:

- Tear film and lacrimation,
- The corneal barrier,
- The iris capillary endothelial barrier,
- The epithelial barrier of ciliary body,
- The retinal capillary barrier, and
- The retinal pigment epithelial barrier,

These approaches have some drawbacks such as low efficiency, off-target delivery, and side effects, and they possess short lifespan. Viral vectors, for example, adeno-associated virus and lentivirus are highly effective transfection tools for gene therapy in ophthalmic research.

However, *in situ* drug delivery system underlines the immunogenicity concern, of immunogenicity, broad tissue tropism, carcinogenesis, and genomic insertional mutagenesis in clinical trials, and thus, in the end, it is hoped that physicians and patients will accept only non-viral vectors for treatment.<sup>[6]</sup>

The sol-gel transition can be induced by a shift in PH, temperature, or ion-activated systems. This type of gel combines the advantage of a solution (accurate and reproducible administration of drug) and gels (prolonged residence time) for enhancing ocular bioavailability.

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## INJECTABLE HYDROGELS

- Hydrogels are water-swollen polymeric structures cross-linked together and cross-links produced through:
  - Chemical reaction to form covalent bonds.
  - Entanglement of polymers.
  - Hydrogen bonding and Van der Waals forces.

### Formulation and Gelation

The major components of an injectable hydrogel are hydrophilic, synthetic, or naturally derived polymers that are cross-linked *in situ* by a variety of mechanisms.<sup>[7,8]</sup> The synthetic polymers may be cross-linked hydrophilic homopolymers or copolymers such as polyvinyl alcohol (PVA), polyethylene glycol, poly(N-isopropylacrylamine) (PNIPAAm), or Pluronic® F-127.

The features of these materials and related gelation approaches are summarized in Table 1.

The major naturally derived polymers used for injectable hydrogels include polysaccharides (alginate, chitosan [CS], and hyaluronic acid) and proteins in ophthalmology, which are biocompatible and have low toxicity.<sup>[9,10]</sup>

### Advantages of *In Situ* Ocular Drug Delivery System

- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time.<sup>[11]</sup>
- Drug effect is prolonged, and hence, frequent instillation of drug is not required.<sup>[12]</sup>
- For patient compliance and enhance therapeutic performance of drug.
- Generally more comfortable than insoluble or soluble insertion.
- System provides ease of administration.<sup>[13]</sup>

## Ideal Characteristics of Polymers for Preparation of *In Situ* Ophthalmic Gels

- It should be biocompatible.
- It is capable of adhering to the mucus membrane.
- Preferred pseudoplastic behavior of polymer.
- Good tolerance and optical clarity are more preferred.
- It should influence the tear behavior.
- The polymer should be capable of decreasing the viscosity with increasing shear rate<sup>[14]</sup>

### Mechanism of *In Situ* Gels

#### *In situ* formation based on physical mechanism swelling

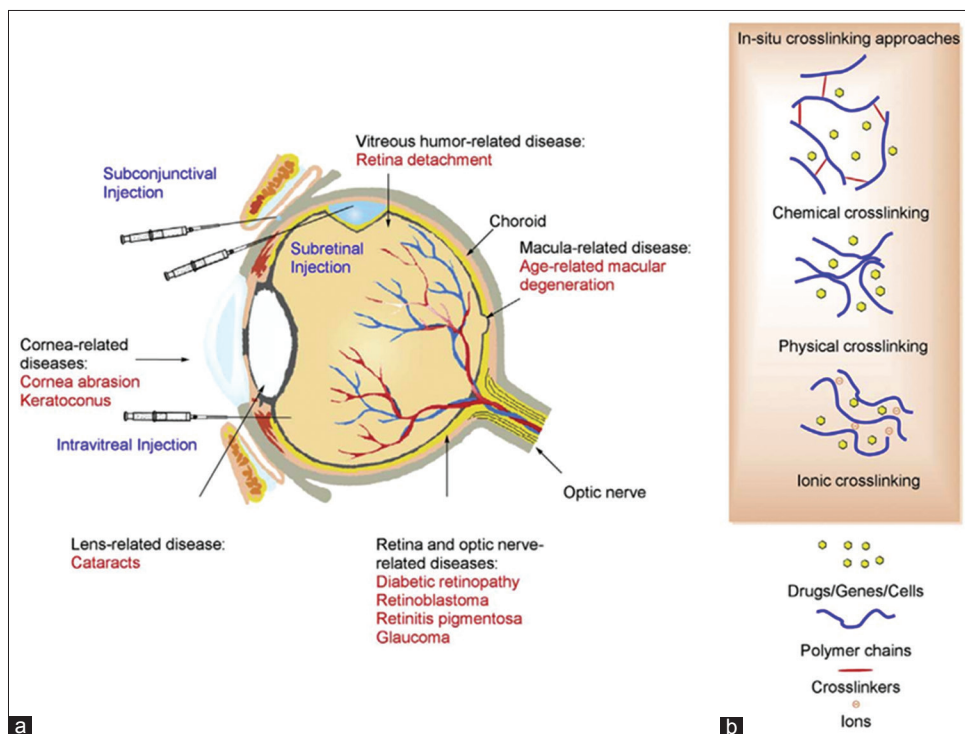
*In situ* formation may also occur when material absorbs water from surrounding environment and expand to desired space. One such substance is myverol (glycerol monooleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded *in vivo* by enzymatic action.

#### Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N- methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.

#### *In situ* formation based on chemical reactions mechanism

Chemical reactions that result *in situ* gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.<sup>[15]</sup>



**Figure 1:** (a and b) Anatomical structure of an eye with related eye disease and formation of *in situ* gelation in injectable hydrogels for ophthalmic disease treatment

## Various approaches of insitu gelation pH triggered insitu gelation

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH-sensitive polymers. The pH is an important signal, which can be addressed through pH-responsive materials. Gelling of the solution is triggered by a change in pH at pH 4.4 and the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH 4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel. The polymers with a large number of ionizable groups are known as polyelectrolyte. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups but decreases if polymer contains weakly basic (cationic) groups.<sup>[16]</sup>

## Temperature triggered insitu gel

Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control but also easily applicable both *in vitro* and *in vivo*. In this system, gelling of the solution is triggered by change in temperature, thus sustaining the drug release. These hydrogels are liquid at room temperature (20–25°C) and undergo gelation when in contact with body fluids (35–37°C), due to an increase in temperature. The use of biomaterial whose transitions from sol-gel are triggered by an increase in temperature is an attractive way to approach *in situ* formation.<sup>[17]</sup>

## Ion activated insitu gelation

In this method, gelling of the solution instilled is triggered by a change in the ionic strength. It is assumed that the rate of gelation depends on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence of the mono- or di-valent cations typically found in the tear fluids. The electrolyte of the tear fluid, and especially, Na<sup>+</sup>, Ca<sup>2+</sup>, and Mg<sup>2+</sup> cations is particularly suited to initiate gelation of the polymer when instilled as a liquid solution in the conjunctival cul-de-sac. The polymer which shows osmotically induced gelation is gelrite or gellan gum, hyaluronic acid, and alginates.<sup>[18]</sup>

## Evaluation of In Situ Gel

These formulations were evaluated for clarity, pH, gelling capacity, drug content, rheological study, *in vitro* diffusion study, isotonicity, *in vivo* ocular testing in rabbits, and accelerated stability studies. The pH of *in situ* gel solution should be 7.4 for all the formulations. The formulation should have an optimum viscosity that will allow for easy instillation into the eye as a liquid (drops), which would undergo a rapid sol-to-gel transition (triggered by pH, temperature, or ion exchange).

## Test for clarity test / appearance

The formulations were observed for general appearance, i.e., color and odor and for the presence of suspended particulate matter. The clarity of the preparation was checked using against black and white background.<sup>[15]</sup>

## Determination of pH

The pH of all formulations was recorded using a calibrated digital pH meter immediately after preparation.

## Gelling capacity

The gelling capacity is determined by placing a drop of the formulation in a vial containing 2.0 ml of freshly prepared simulated tear fluid and visually observed. The time taken for its gelling is noted.

## Drug content

The drug content was determined by accurately placing 100 µl of formulations in a test tube and suitably diluted with simulated tear fluid (STF) to obtain a concentration of 10 µg/ml. Using UV-Visible spectrophotometer, the drug concentration was determined.<sup>[15]</sup>

## Rheological studies

Viscosity and rheological properties of *in situ* forming drug delivery systems can be assessed using Brookfield rheometer or some other type of viscometers such as Ostwald's viscometer. The viscosity of these formulations should be such that no difficulties are envisaged during their administration by the patient, especially during parenteral and ocular administration.

## In vitro drug release studies

*In vitro* release study of *in situ* gel solution is carried out using Franz diffusion cell. The formulation placed in donor compartment and freshly prepared simulated tear fluid in receptor compartment. Between donor and receptor compartments, dialysis membrane is placed (0.22 µm pore size). The whole assembly is placed on the thermostatically controlled magnetic stirrer. The temperature of the medium is maintained at 37°C ± 0.5°C. 1 ml of sample is withdrawn at a predetermined time interval of 1 h for 6 h, and the same volume of fresh medium is replaced. The withdrawn samples are diluted in a volumetric flask with respective solvent to specific volume and analyzed by UV spectrophotometer at respective nm using reagent blank. The drug content is calculated using the equation generated from standard calibration curve, and then, the % cumulative drug release is calculated. The data obtained are further subjected to curve fitting for drug release data.

## Texture Analysis

The consistency, firmness, and cohesiveness of *in situ* gel are assessed using texture profile analyzer which mainly indicated gel strength and easiness in administration *in vivo*. Higher values of adhesiveness of gels are needed to maintain an intimate contact with mucus surface.

## Sterility testing

Sterility testing was performed for aerobic and anaerobic bacteria and fungi using fluid thioglycolate and Soybean Casein digest medium, respectively, as per the Indian Pharmacopoeia. The method used for sterility testing was direct inoculation method. 10 ml culture was added to 100 ml of culture medium. Both media were kept for incubation at 32°C for 7 days and observed for any microbial growth.<sup>[19]</sup>

## Isotonicity evaluation

Isotonicity is an important characteristic of the ophthalmic preparations. Isotonicity should be maintained to prevent tissue damage or irritation of the eye. All ophthalmic preparations undergo isotonicity testing. Formulations mixed with few drops of blood and observed under microscope at ×45 magnification and compared with standard marketed ophthalmic formulation.

## Ocular irritancy test

The Draize irritancy test is designed for the ocular irritation potential of the ophthalmic product before marketing. According to Draize test, the amount of substance applied to the eye is normally 100  $\mu$ l placed into the lower cul-de-sac with the observation of the various criteria made at a designed required time interval of 1 h, 24 h, 48 h, 72 h, and 1 week after administration. Three rabbits (male) weighing 1.5–2 kg are used for the study. The sterile formulation is instilled twice a day for 7 days, and a crossover study is carried out (3-day washing period with saline was carried out before the crossover study). Rabbits are observed periodically for redness, swelling, and watering of the eye.

## Accelerated stability studies

Formulations are placed in ambient color vials and sealed with aluminum foil for a short-term accelerated stability study at  $40 \pm 2^\circ\text{C}$  and  $75 \pm 5\%$  RH as per the International Conference on Harmonization states guidelines. Samples are analyzed every month for clarity, pH, gelling capacity, drug content, rheological evaluation, and *in vitro* dissolution. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.<sup>[20]</sup>

## INJECTABLE HYDROGELS IN OPHTHALMIC TREATMENT

Major ophthalmic diseases and disorders include age-related macular degeneration (AMD), cataracts, cancers, corneal wear, DR, glaucoma, inflammation, keratoconus, retinal detachment, and retinitis pigmentosa. The following section is a summary and a discussion of the progress on the research on injectable hydrogels in the treatment of the aforementioned diseases and disorders.

### Corneal Abrasion and Keratoconus Cause

The epithelial surface of the cornea is vulnerable to mechanical wear and may cause temporary pain and reduced vision. The light abrasion may be restored by the reconnection of epithelium cells, but severe damage may require antibiotics and a sealant to prevent infection and further damage. Keratoconus is a common progressive degenerative eye disorder with structural changes in thinning cornea and causes a conical shape of cornea, thus deflecting the light way to the retina. The severe distortion of vision, streaking, and sensitivity to all light are the common symptoms in the keratoconus patient.<sup>[21]</sup>

### Treatment

PEG-based homopolymers and copolymers are ideal for this purpose. A PEG-based doxycycline-laden transparent hydrogel can be formed *in situ* rapidly using thiol reaction and evaluated for their wound healing application.

The PEG hydrogel can resist the deformation under shearing force and prolong the release of drug up to 7 days. A significant reduction of matrix metalloproteinase-9 was demonstrated by immunofluorescence studies and histology studies, which exhibited superior corneal healing compared to conventional topically administered solution.<sup>[22]</sup>

## Cataracts

### Cause

Cataracts are the greatest cause of blindness worldwide, and over 50% of blindness and 30% of vision impairment are the result of cataracts. The cause is a slowly developing clouding of the lens of one eye or both eyes.<sup>[23]</sup> This disease is considered as a consequence of aging and other factors (e.g., trauma, radiation, and excessive exposure to sunlight). The current treatment of cataracts is surgical, i.e., the removal of the cloudy lens.<sup>[24]</sup> Hydrogels have been used as a replacement lens after surgical incision and have similar requirements as the previously discussed corneal surgery sealants.

### Treatment

Synthetic polymers work better than naturally derived polymers as wound dressings and sealants. PEG hydrogel polymers are primarily used because they have a long safety record, biocompatibility, and a high water content, which are similar to that of the eye. PEG-based hydrogels can be engineered to meet mechanical and biological requirements for applications as a sealant.<sup>[25]</sup> Studies exist on the PEG-polymerized adherent ocular bandage during transient fluctuations of the IOP.<sup>[26]</sup>

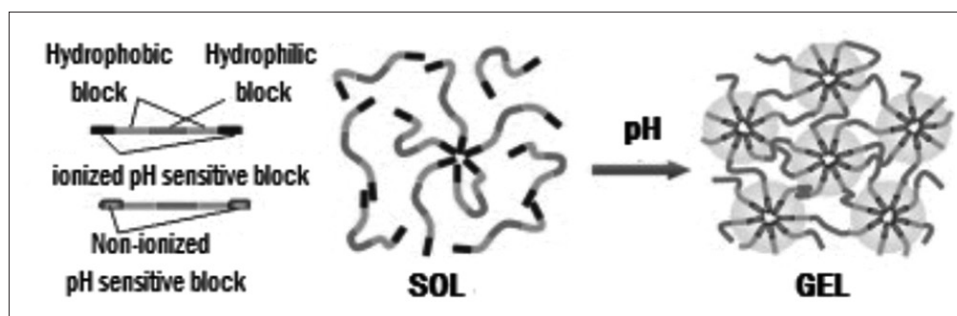
## Glaucoma

### Cause

Glaucoma is the second major cause of blindness in the world after cataracts. It is caused by increasing intraocular pressure with imbalance between aqueous humor production and drainage of aqueous humor through trabecular meshwork and scleral venous sinus [Figure 5], thus putting pressure on the optic nerve that results in the impairment of the nerve system and a loss of vision.<sup>[27]</sup> Medications such as Timolol Maleate, Xalatan, and pilocarpine are commonly used for glaucoma treatment in the form of eye drops. However, conventional administration methods such as eye drops have a drawback of low bioavailability (<5%), and intravitreal injections have a relatively short retention time; therefore, hydrogels may provide sustained release and improve bioavailability.<sup>[1]</sup> For instance, OTX-TP from Ocular Therapeutix is under Phase 3 clinical trial for the treatment of glaucoma. There are also microcatheter-based drainage and laser-based surgical methods in medical practice that uses a hydrogel as a sealant of incision similar to cataract surgery.<sup>[28]</sup>

### Treatment

The delivery of IOP management drugs utilizes both synthetic and naturally derived injectable hydrogels. A thermoresponsive copolymer, PNIPAAm-CS, has been investigated for ocular drug delivery. PNIPAAm-CS featured a low critical solution temperature of  $32^\circ\text{C}$ , which is lower than physiological temperature.<sup>[1]</sup> Timolol Maleate, a useful drug in glaucoma treatment, was studied with the hydrogel and showed a release profile with a larger area under the curve compared with conventional eye drops and reached a final concentration of  $11.2 \mu\text{g}/\text{mL}$ . The MTT assay showed the minimal toxicity of a Timolol Maleate-laden hydrogel with 0.5–400 g/mL concentration of polymers. The PNIPAAm-CS hydrogel has the potential to extend the drug released into a glaucomatous eye and more effectively reduce IOP than conventional eye drops. In another study, gelatin was grafted with carboxylic end-PNIPAAm through a carbodiimide coupling reaction *in situ* to produce a delivery system which was designed for the administration of



**Figure 2:** pH-sensitive system

intracameral anti-glaucoma medication.<sup>[29]</sup> The hydrogel had superior thermal gelation and adhesion and was biodegradable in the presence of an enzyme. Cytotoxicity studies suggested that the anterior segment with *in situ* forming gels had good proliferation and minimal inflammation. The hydrogel had a high encapsulation (62%) and cumulative release ratio (95%), and the subsequent degradation of the gelatin network was progressive. The *in vivo* efficacy of the delivery carrier was evaluated in a rabbit glaucoma model, and the intracameral administration of pilocarpine using a hydrogel was found to be more effective than traditional eye drops and injection of free drug. Furthermore, the hydrogel extended the reduction of IOP and pharmacological responses related to reduced-IOP, such as miotic action and stable corneal endothelium density.

Gelatin and CS can be crosslinked using different agents, including genipin which was tested to deliver Timolol Maleate. The gelatine and CS gels obtained with the aid of genipin were safe and useful for the controlled intraocular drug release.<sup>[30]</sup> The alginate was employed as a rapidly forming injectable hydrogel and was consequently used to release pilocarpine and Kelton.<sup>[31]</sup> *In vitro* studies indicated that pilocarpine was released slowly from an alginate gel through diffusion from the gel and the guluronate residue ratio of alginate governed the release rate. The rabbit eyes were treated with injectable hydrogel composed of alginate loaded with pilocarpine, and the lowered IOP indicated a significant extension of the pressure-reducing effect.

## Retinal Detachment Cause

Retinal detachment is caused by fluid leaking behind the RPE, and the treatment includes removal of the vitreous humor and filling it with other materials.<sup>[1]</sup> The surgical treatment for retinal detachment requires vitreous tamponade-like agents to fill the volume and restore the IOP, allowing the detached neurosensory retina to attach to the RPE. The most commonly used vitreous tamponade agents in clinical surgery include sulfur hexafluoride, perfluorocarbon gasses, perfluorocarbon liquids, and silicone-based oils. However, no material is currently clinically available as a long-term vitreous substitute. The development of a substitute for the vitreous body remains challenging in ophthalmology research but is interesting to investigate. A hydrogel may be a superior choice as a substitute for the vitreous humor by employing a polymer solution to fill a potential irregular cavity using a minimally invasive technique, providing a similar refractive index and viscosity as the natural vitreous humor.<sup>[32]</sup>

## Treatment

The PEG- and PVA-based injectable hydrogels are desirable candidates for their stability, optical transparency, and matching mechanical properties. In a study, the foldable capsular vitreous body (FCVB) was injected with a PVA hydrogel to serve as a long-term vitreous substitute. The PVA hydrogel was crosslinked by gamma irradiation and showed good viscoelasticity and biocompatibility on L929 cell lines and maintained constant IOP and retinal morphology. The hydrogel inside the FCVB remained transparent and supported the retina 180 days after injection. The PVA hydrogel with improved stable performance may be utilized as a vitreous substitute; however, gamma radiation crosslinking has to be carefully handled.<sup>[33]</sup> Another example reported an injectable vitreous substitute composed of thermosensitive amphiphilic polymer poly(ethylene glycol) methacrylate (PEG-MA), which could form a transparent gel *in situ*.<sup>[34]</sup> The hydrogel allows more transmission of visible light compared to natural vitreous and exhibits mechanical stability under temperature changes and shearing force. The hydrogel was biocompatible both *in vitro* and *in vivo* and kept IOP at a desirable level. Furthermore, an *in situ* gelation system based on  $\alpha$ -PEG-MA and a redox-initiated radical crosslinking reaction was developed as a vitreous substitute.<sup>[35]</sup> The studies characterized reaction kinetics, gelation time, rheological properties, and swelling behavior in detail. It has been shown that the system formed a transparent gel in the vitreous cavity, and the inflammation response caused by injection could be controlled in a rabbit model.

## DR Cause

DR is caused by choroidal blood vessel damage from diabetes which finally leads to partial or complete loss of vision. Treatment includes laser surgery, corticosteroid injection, and antiangiogenesis treatment. The monoclonal anti-vascular endothelial growth factor (VEGF) drugs Avastin® (Bevacizumab), Lucentis® (Ranibizumab), and Eylea® (Aflibercept) are the most commonly used drugs for DR. A wet AMD treatment in the clinic is a recent antiangiogenesis treatment; however, it has a short lifespan through intraocular injection and required repeated delivery. An injectable hydrogel may improve delivery efficiency and render sustained delivery. The current research on DR focuses on improving delivery efficiency of anti-VEGF and diabetic management drugs (heparin and some growth factors) for diabetes treatment, as well as for stem cells for regeneration in the future.<sup>[36,37]</sup> The hydrogel-based VEGF delivery system will be discussed along with AMD.

## Treatment

The fibrin with a bi-domain peptide incorporated has a drug release profile which is controlled through reversible binding, and the system can form a gel *in situ*.<sup>[37]</sup> The peptide sequesters affinity to heparin within the matrix and can slow the release of any heparin binding protein such as fibroblast growth factor (FGF) because it reversibly binds the heparin. This fibrin gel has been tested as the controlled delivery vehicle of multiple factors, and the peptide sequences affinity to heparin can slow the release of protein reversibly bind the heparin.<sup>[37]</sup> A recent study introduced an ECM-derived hydrogel for heparin and growth factor delivery.<sup>[38]</sup> The system immobilizes growth factors on a hydrogel using a variety of interactions (e.g., chemical bonding or growth factor binding domains) to increase their stability and activity. The hydrogel with sulfated glycosaminoglycan content in a study was derived from a decellularized pericardial ECM and could bind with basic fibroblast growth factor (bFGF). Delivery of bFGF both *in vitro* and *in vivo* from a hydrogel increased the retention compared to the delivery in standalone collagen. An intramyocardial injection in a rodent infarct model showed improved neovascularization, and the newly formed blood vessel was anastomosed with the existing vasculature. Thus, a decellularized ECM hydrogel provided a platform for the incorporation of heparin-binding growth factors for the regeneration of the retinal structure.

## Intraocular Cancers

The major types of intraocular cancers which occur in adults are melanoma and lymphoma, and retinoblastoma is a relatively rare cancer in children.<sup>[39]</sup> The cause of intraocular cancer may vary, and current intraocular cancer treatment includes chemotherapy, radiation therapy, targeted therapy, and surgery.<sup>[40]</sup> Chemotherapy drugs used to treat ocular cancers include dacarbazine, vincristine, etoposide, carboplatin, doxorubicin, and cisplatin. However, chemotherapy incompletely eradicates the tumors because high doses are not delivered to the tumor. The role of an injectable hydrogel in cancer treatments is mainly focused on the localized delivery of chemotherapy or chemoimmunotherapy drugs. Carboxymethyl CS hydrogels were crosslinked by genipin and studied in terms of the *in vitro* drug release of 5-fluorouracil

(5-FU) and bevacizumab.<sup>[1]</sup> The major proportion of 5-FU was released from the drug hydrogels within 8 h, but the bevacizumab was released in a slow manner, it was < 20% after 53 h. An *in vivo* evaluation in rabbits indicated that the drug-laden hydrogels were non-toxic and biodegradable.

## Treatment

Chondroitin 6-sulfate (C6S) was incorporated with poloxamer to form a transparent hydrogel.<sup>[41]</sup> The copolymer was prepared by EDC crosslinking, the gelation temperature of the hydrogel was determined to be body temperature, and the gelation temperature could be lowered by decreasing the C6S content and elevating the polymer concentration. The release of drug from the hydrogel was sustained *in vitro*, and the releasing rate of drug can be altered by the C6S content in the system as the result of the *in situ* gelation. The C6S-g-poloxamer coated surface was observed as biocompatible and suggested from human lens cell (B3) transformed shapes after 2 days. These nanoscale hydrogels may be effective drug carriers for chemotherapy drugs through topical or intraocular administration.

## Age-related Macular Degeneration

### Cause

AMD is the most commonly seen age-related ocular disease in the western world, is most prevalent in those over 55 years of age, and results in visual deficits. AMD can be divided into two categories: Atrophic (as known as dry AMD, 90% prevalence) and exudative (wet AMD, more severe) AMD. Dry AMD is a consequence of drusen accumulation, and the wet form is associated with abnormal angiogenesis [Figure 3]. Currently, no effective treatment exists for dry AMD, and wet AMD may be treated with anti-VEGF drugs with injections directly into the eye once a month, with no approach to recover lost vision.<sup>[42,43]</sup> Similar to DR, antiangiogenesis approaches are effective in preventing the progression of the disease and have been approved by the FDA for wet AMD treatment. However, the recovery of lost or impaired vision remains elusive. From recent studies it has been revealed that ROS is associated with both dry and wet AMD, thus controlling ROS which may become an effective approach to prevent the progression of AMD.<sup>[44]</sup> The long-term sustained intraocular

**Table 1: Major polymer components in ophthalmic injectable hydrogels**

Synthetic polymer	Gelation method	Advantages	Disadvantages
PAAC	pH change	Controlled swelling behavior	Cytotoxicity and cause inflammation
PEG	Temp, chemical cross-linking	Easy to crosslink, biocompatible, stable	Non-biodegradable
Pluronic F-127	Temperature	Biocompatible, controlled properties	Non-biodegradable, weak mechanical properties and stability
PVA	Chemical crosslinking	Stable, biodegradable	Not stimuli-responsive, crosslinkers may be toxic
Natural polymers	Gelation method	Advantages	Disadvantages
Alginate	Chemical/ionic crosslinking	Rapid gelation, good mechanical properties	Poor cell adhesion
CS	Chemical crosslinking	Easy to modify	Poor solubility at neutral PH
Collagen	Chemical crosslinking	Cell adhesion, biocompatible	Difficult to dissolve, susceptible to degradation
Dextran	Chemical crosslinking	Biocompatible, easy to crosslink, large capacity	May cause side effect <i>in vivo</i>
Gelatin	Chemical crosslinking	Easy to dissolve, biocompatible	Weak mechanical properties, susceptible to degradation
Hyaluronic acid	Chemical crosslinking	Easy modification, bioactive	High viscosity, susceptible to degradation

PEG: Polyethylene glycol, CS: Chitosan, PVA: Polyvinyl alcohol

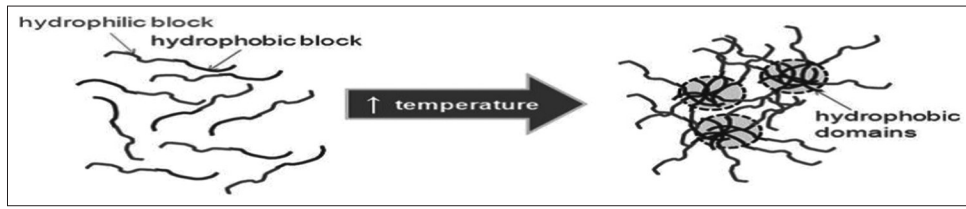


Figure 3: Mechanism of temperature-sensitive system

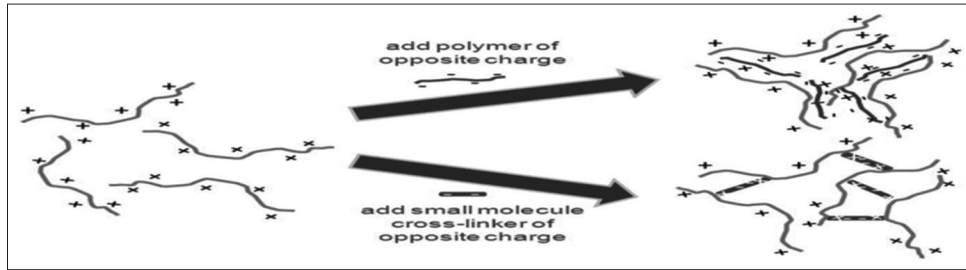


Figure 4: Mechanism showing ion-activated system

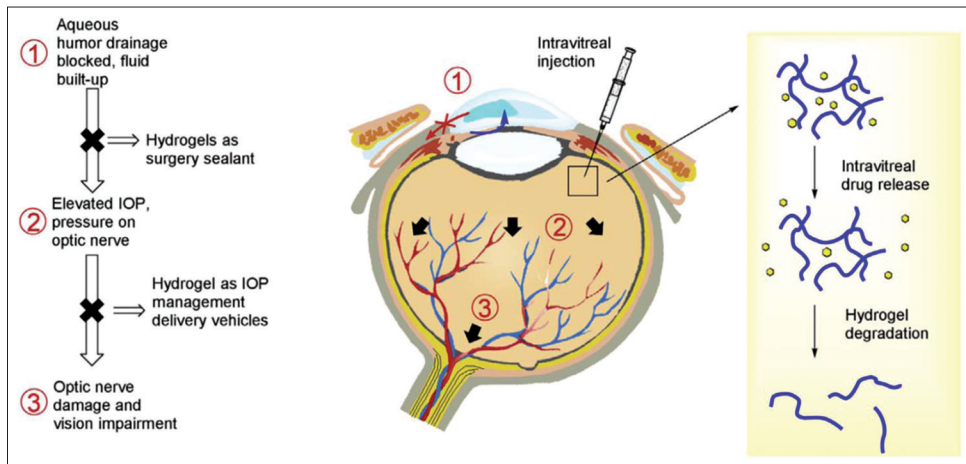


Figure 5: Pathophysiology of glaucoma and current treatment with injectable hydrogels

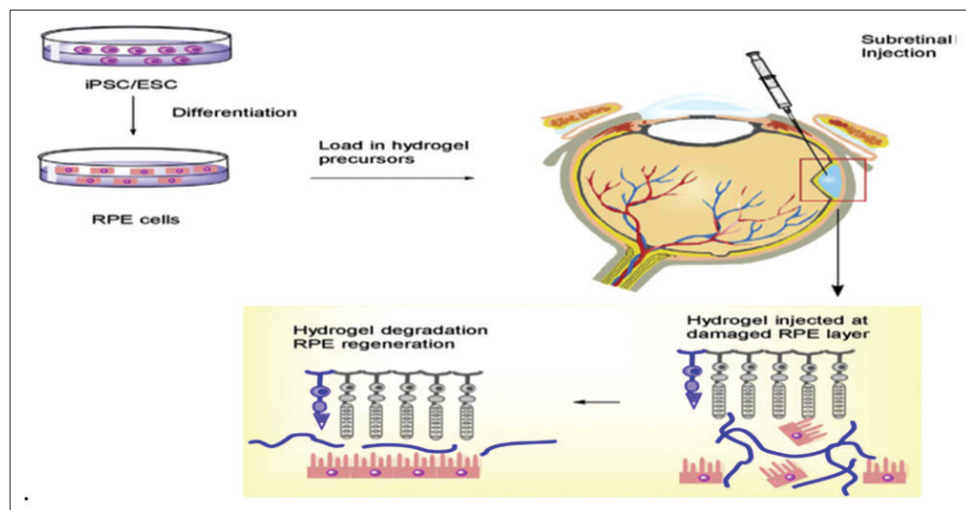


Figure 6: Stem cell treatment with an injectable hydrogel for retina photoreceptor regeneration

delivery of robust antioxidants and/or antiangiogenic agents may be considered as the best option for both dry and wet AMD.<sup>[45]</sup>

## Treatment

An injectable hydrogel was developed from alginate and CS for the potential intraocular delivery of antibody drugs. This polysaccharide cross-linked hydrogel had a degradation rate associated with the oxidized alginate content. Encapsulated Avastin had an initial burst release from hydrogels and then sustained release in 3 days, and the increase of the oxidized alginate concentration lowered the release rate of Avastin from the hydrogel.<sup>[46]</sup>

## Stem cell treatment

Similar to DR, an alternative treatment strategy under investigation for dry AMD utilizes the transplantation of RPE or photoreceptor cells. The approach involves the delivery of RPE cells under the retina to restore damaged vision [Figure 6]. The injection of RPE cells into the subretinal space seems to be promising, although post-injection cellular positioning and cell viability may be issues. The use of an injectable hydrogel for cell delivery may overcome those issues by providing physical support for cells and preventing cell death.<sup>[47,48]</sup> Furthermore, transplantation may be conducted in a minimally invasive way, without surgery in RPE sheet implantation. Furthermore, it has been found that ESC/iPSC is capable of replacing damaged retinal cells. Neural stem cells (NSC) may potentially become replacement cells and be mediators of treatment. Injectable hydrogels based on alginate, collagen, or CS are being developed and show a continuous, slow, and low *in vivo* release over several weeks.<sup>[1,47]</sup> However, the loading capacity of a hydrogel is limited, so during the treatment of AMD, and repeated injection of hydrogel for sustained release remains a great hurdle to FDA approval. Safety issues (incidence or adverse events) occurred in an earlier trial of stem cell treatments, which rendered this potential therapy more unpredictable.<sup>[47,48]</sup>

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