

OCCULAR DRUG DELIVERY SYSTEM: NOVEL TECHNIQUES OF HYDROGELS TARGETING SYSTEM ON POSTERIOR SEGMENT DISEASE

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Abstract- Ocular drug delivery has been a major challenge due to the unique anatomy and physiology of the eye. Treatment for Posterior segment disease still remains a huge task for formulation scientist. Ocular drug delivery using injectable hydrogel involves the administration of therapeutic agents directly into the eye in the form of gel. Ocular drug delivery has been a major challenge due to the unique anatomy and Hydrogels are generally a series of relatively hydrophilic polymers with the ability to form three dimensional across linked network and preserve large amount of water. Hydrogels are multifunctional ophthalmic drug delivery systems capable of extending drug residence time and sustaining release of drugs. An injectable hydrogel is generally based on the idea that some biomaterials can be injected as liquid into human body. Thermogels, or thermo-responsive hydrogels, are a subclass of the supramolecular hydrogels that gelate via hydrophobic interactions. Thermogels are temperature-sensitive hydrogels that can transition from a liquid to a gel state. In ocular drug delivery, thermogels are used to improve drug retention and sustained release on the ocular surface. In this review, injectable hydrogel, posterior segment diseases and corresponding Treatments are briefly introduced. In addition of temperature responsive hydrogel also described in brief.

Key words: ODDS, Ocular drug delivery, Injectable hydrogel, Posterior segment, Thermogel.

INTRODUCTION

Eyes are the window to the outside world and thus become an important part of our body. Rephrase Ocular drug delivery has been one of the most exciting and challenging activities that pharmaceutical scientists have faced over the past two decades. Old dosage forms of ophthalmic solutions, ointments and suspensions no longer provide the necessary therapeutic effect for a number of today's toxic diseases. Treating diseases in the posterior remains a herculean task for formulation scientists. Tight junctions of the blood-retinal barrier (BRB) systemically limit drug penetration into the retina. Intravitreal injections are the only clinical option for treating posterior segment disease (e.g., retina and choroid). The burden of such injections on patients and the healthcare system is enormous. For example, nearly 20 million anti-vascular endothelial growth factors. Injections are given into the vitreous every year to treat wet age-related macular degeneration. The World Health Organization reports that at least 2.2 billion people worldwide have visual impairment Drug treatment is the mainstay of treatment for most eye diseases. Delivering drugs to ocular tissues at desired therapeutic concentrations without harming healthy tissue is a current research hot spot. Hydrogels are generally a series of relatively hydrophilic polymers with the ability to form three-dimensional cross-linked networks and conserve large amounts of water. Recently, hydrogels are emerging as a biological alternative to contact lenses, hygiene products, tissue engineering scaffolds, wound dressings, and biosensors, show a promising future in the development of ophthalmic devices. Accordingly, it is time for us to present the most recent advances in the use of hydrogels in ophthalmic applications. Injectable hydrogel systems have made notable advances in biomedical applications in recent years These biomaterials offer a multitude of benefits, including controlled release, targeted release, and improved mechanical properties. This article reviews the latest hydrogel formulations and their associated chemistries for use in eye diseases.

ANATOMY AND PHYSIOLOGY OF EYE

The eye is a spherical structure with a wall of three layers; the outer part of the sclera, the middle layer of the choroid, the ciliary body and iris and the inner part of the neural tissue layer of the retina. The sclera is a tough, fibrous covering that protects the inner tissues of the eye. It is white except for the clear front area and the cornea, which allows light to enter the eye. The anatomical structure of the eyeball can be divided into anterior and posterior parts. The anterior part includes the cornea, conjunctiva, iris, ciliary body, aqueous humor, and vitreous body, while the posterior part includes the sclera, choroid, retina, and vitreous body. The physiology of the eye includes a transparent cornea, lens, and

avascular lens. Oxygen and nutrients are transported to this avascular tissue by aqueous humor, which has a high oxygen content and an osmotic pressure similar to blood. The cornea has many free nerve endings. The cornea and sclera resist the intraocular tension that is continuously maintained in the eye.

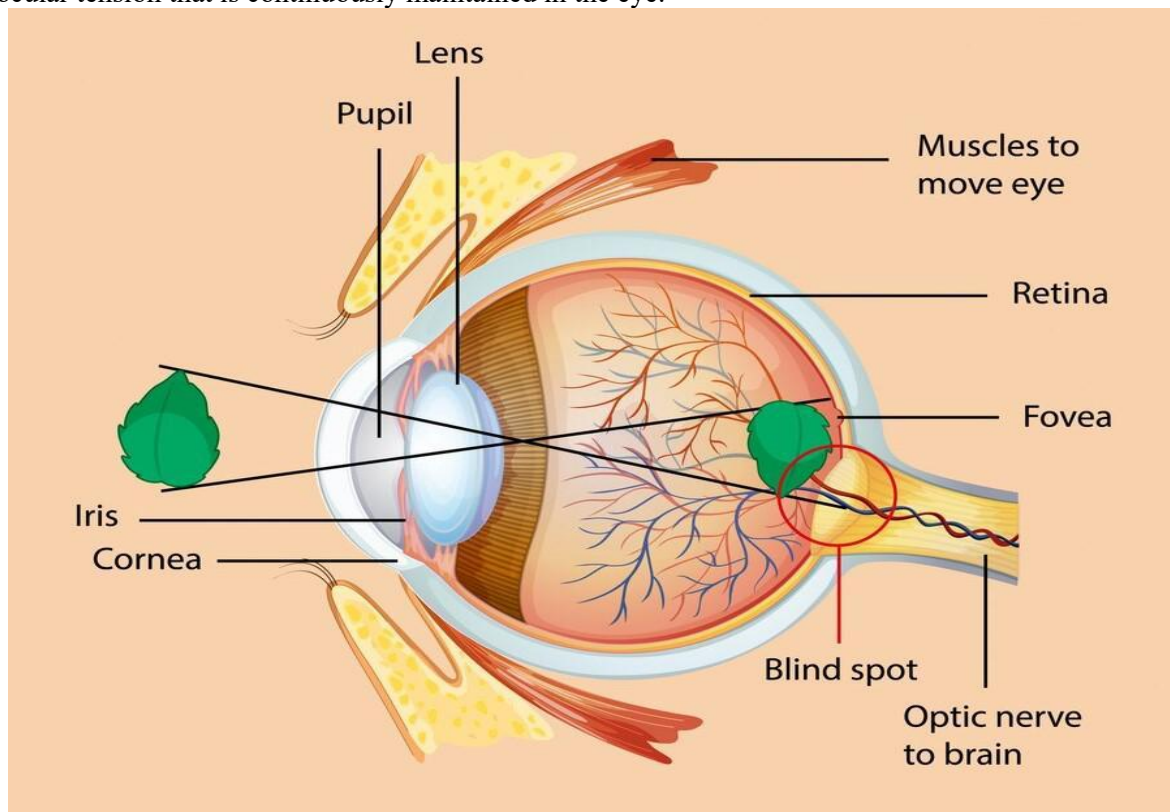


Figure: 1 Human Eye

INJECTABLE HYDROGEL

Considers physiological barriers of the eye, challenges in effectively delivering a therapeutic product line, and overall patient compliance treatment options, innovative hydrogel delivery methods are needed. field of ophthalmology. Hydrogel is a type of material with properties favorable for sustained drug release Composed of a three-dimensional network of hydrophilic polymer chains, hydrogels have a high-water retention capacity. Their properties such as reactivity to heat, pH and light stimulation can be modified through the monomers and cross-linking agents used. Hydrogel is a hydrophilic polymer system capable of retaining a significant amount of water and swelling in an aqueous environment. However, due to their three-dimensional (3D) cross-linked structure, they are insoluble in water and biological fluids. In addition, injectable hydrogels have attracted great interest due to their good biocompatibility, simple handling, ease of formation, and noninvasive drug delivery via injection. Injectable hydrogels are potentially attractive for clinical applications because they can significantly reduce patient discomfort, risk of infection, recovery time, and treatment costs, especially in the wound does not heal. Additionally, introducing nanomaterials into hydrogels also improves their injectability and thinning properties. Since the size and shape of the injectable hydrogel is determined by its local environment, good surface contact between the hydrogel and adjacent tissue is usually achieved, allowing the drug to elute directly into the local tissue and, in some cases, facilitating healing., injectable and degradable material. In situ, solutions can change from a solution to a semi-solid gel in response to environmental stimuli such as temperature, pH, pressure and/or ionic strength (Bi and Liang, 2016) has been the subject of research and application., hydrogels have been extensively studied due to their simpler application and lower tissue side effects compared to other stimuli-responsive gelation systems. To form an ideal studied due hydrogel system for drug delivery, temperature-responsive polymers must form a liquid solution at room temperature and transform into a non-flowing gel once introduced into the body at birth temperature (32 to 37°C).

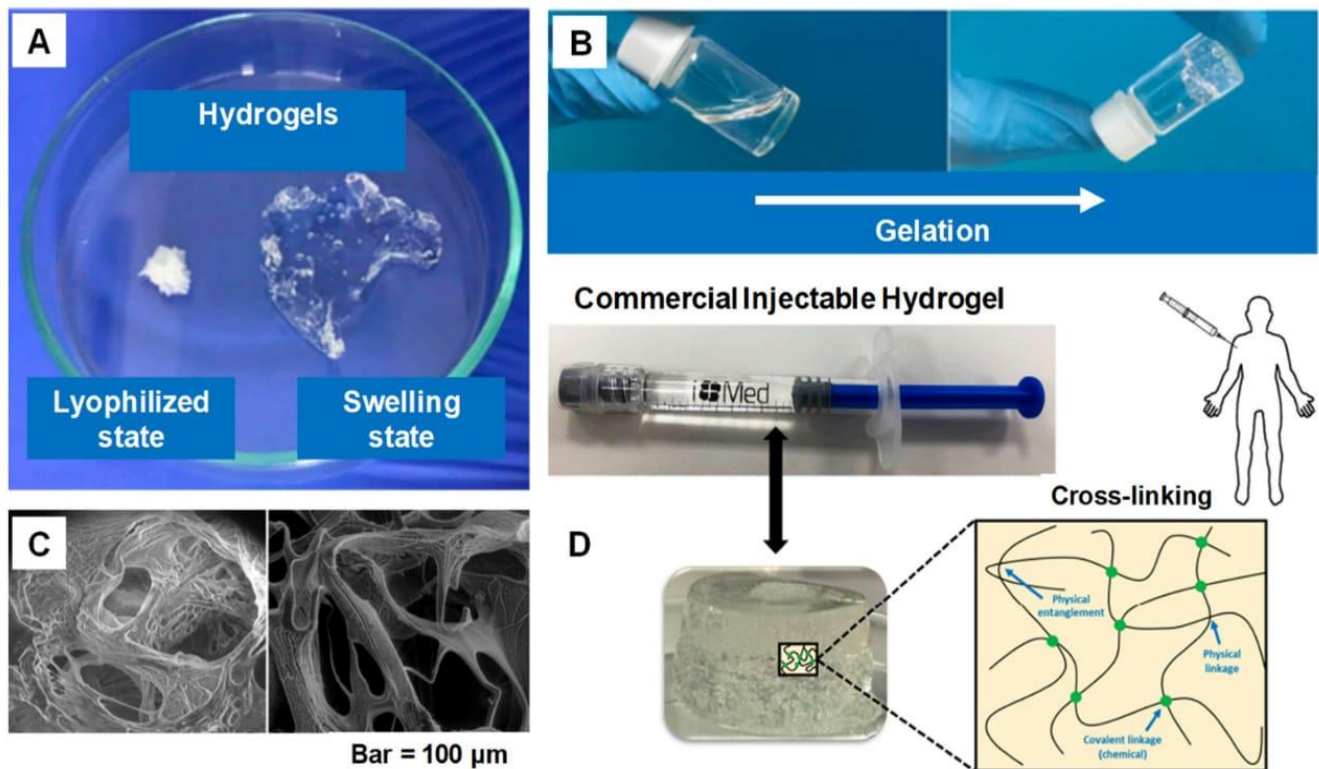


Figure: 2 (A) Swelling ability of hydrogel in lyophilized state. (B) Example of measuring gelation time using the inverted flask method. (C) Cross-sectional SEM image of freeze-dried injectable hyaluronic acid hydrogel. (D) Physical interactions and chemical bonding of the chemical structure of injectable hydrogels.

Properties of injectable hydrogel

Thermogels are composed of amphiphilic polymers with both hydrophilic and hydrophobic parts, which allow them to undergo a sol-gel phase transition usually refers to a heat-sensitive hydrogel that can form a gel at high temperatures and become a liquid again at low temperatures within a certain temperature range. This is in contrast to traditional melt transition behavior. Negative temperature-sensitive hydrogels, which undergo a gel-sol transition upon heating above the lower critical solution temperature (LCST), have been extensively investigated for drug delivery applications. This is because injectable hydrogels have suitable physiological properties for in situ administration into the body due to the following reasons: Rapid temperature injected. Therefore, one of the most important factors to consider is the viscosity of the polymer solution. This is because this property is advantageous for minimally invasive surgery. Some injectable hydrogels induce a variety of inflammatory, immune-mediated responses. Strength and modulus, compressive stress and modulus, shear stress, stiffness, storage and loss. Early or late local or systemic side effects. This indicates that biocompatibility and nontoxicity are important criteria for a good injectable hydrogel system. Another important factor is the porosity of the hydrogel. In this case, highly interconnected networks are preferred because they improve nutrient transfer and adaptation to surrounding tissues. This also affects the correct mechanical properties. (including tensile modulus, fragility, mesh size, and density), because hydrogels must withstand certain deformations that occur in the mechanically dynamic environment within the body. Formulation and Gelation The main components of injectable hydrogels are hydrophilic synthetic or naturally derived polymers that are crosslinked in situ by various mechanisms. Synthetic polymers are crosslinked hydrophilic homopolymers or copolymers such as polyvinyl alcohol (PVA), polyethylene glycol (PEG), poly(N-isopropylacrylamide) (Niam), or Pluronic® F-127. Niam is polymerized from isopropylacrylamide and is also studied due, with a low critical solution temperature (LCST) below physiological temperatures, allowing for rapid gelation. Pluronic® F-127 is a copolymer of polyethylene glycol and polypropylene glycol that is also studied due and biocompatible. The main naturally derived polymers used in injectable hydrogels include ophthalmic polysaccharides (alginate, chitosan, hyaluronic acid) and proteins, which are biocompatible and have low toxicity. Alginate is an anionic polysaccharide that is a linear block polymer of D-mannuronic acid and guluronic acid, which can be cross-linked by divalent ions. Hyaluronic acid (HA) is an anionic polymer consisting of alternating groups of D-glucuronic acid and N-acetyl-D-glucosamine linked by 1,4 bonds, and it plays a role in the regulation of cell adhesion between the ECM and vitreous humor. plays an important role in construction. Cell motility and angiogenesis. Cross-linking is an important parameter in the preparation of hydrogels, leading to improved biomechanical properties through the development of intermolecular network connections. Ideally, crosslinkers should be able to improve mechanical strength and stiffness, be non-toxic, increase enzyme resistance, effectively influence

cell-material interactions, and maintain shape memory. The specific chemical and structural properties of hydrogels have a significant impact on the cross-linking mechanism. Chemical crosslinking methods use covalent bonds between polymer chains to create permanent hydrogels. Crosslinks can be formed by small crosslinking molecules, interpolymer bonds, addition of photosensitive active ingredients, or enzyme-catalyzed reactions. Physically crosslinked hydrogels are prepared without crosslinking moieties or chemical modifications. In contrast, chemically cross-linked hydrogels allow absorption of water and/or bioactive compounds without dissolution, allowing drug release by diffusion. Furthermore, I- was formed using ionic cross-linking (e.g., divalent ion cross-linked alginate or fibrin and factor xiii) and supramolecular interactions (e.g., cyclodextrin) injectable.

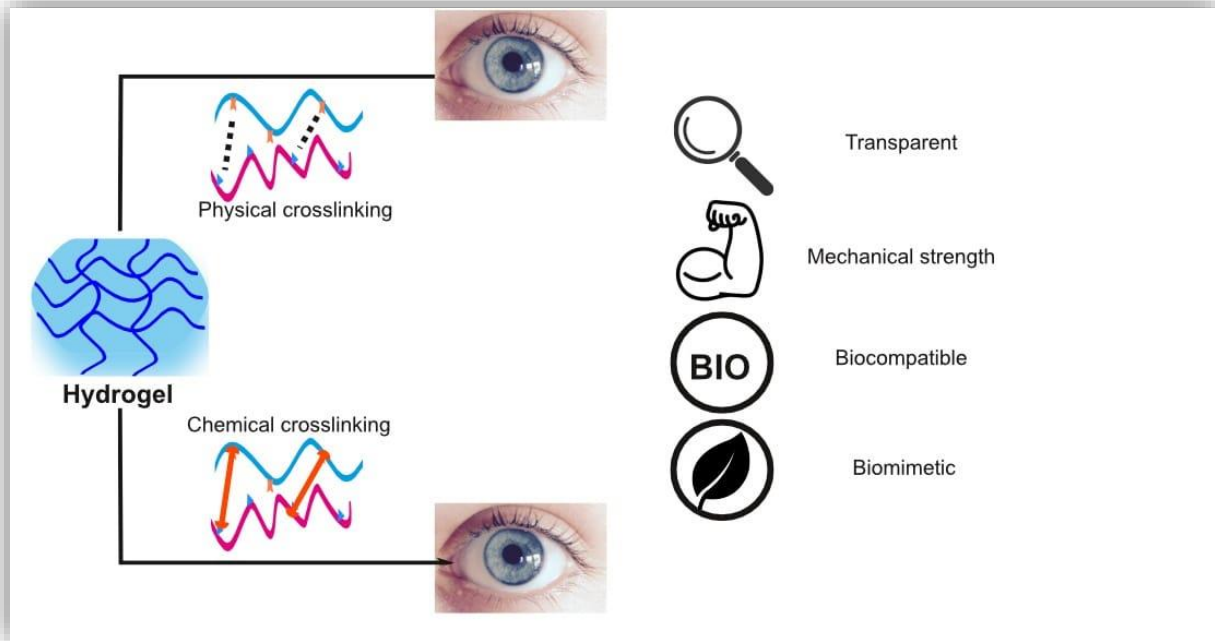


Figure: - 3 Effect of Physical and Chemical Crosslinking of Hydrogel

THERMOGEL

Thermogels, or thermo-responsive hydrogels, are a subclass of the supramolecular hydrogels that gelate via hydrophobic interactions re-induced gelation without requiring organic solvents or chemical reaction. Thermogels can undergo a sol-gel phase transition because they are constituted of amphiphilic polymers with both hydrophilic parts and hydrophobic parts. Thermogels typically refer to thermosensitive hydrogels which can form a gel at a higher temperature and return back to a liquid at a lower temperature within a certain temperature range, which is contrary to the conventional melt transition behavior. Negatively temperature-responsive hydrogels that undergo a sol-gel transition on warming above a lower critical solution temperature (LCST) have been extensively investigated for drug delivery applications, owing to their fast temperature-induced gelation without requiring organic solvents or chemical reaction.

Ocular angiogenic disorders of posterior segment and Treatment

The physiology of the eye is unique. The back of the eye is rich in blood vessels and is sensitive, making treatment difficult to access. The retina, the complex multicellular layer responsible for vision, is the source of many diseases. The most common and serious retinal diseases are diabetic retinopathy (DR) and age-related macular degeneration (AMD), which affect more than 10 million people in the United States, for example.¹ However, the posterior (anti-VEGF) protein requires frequent intravitreal injections of the protein. Some intraocular implants designed to treat serious diseases at the back of the eye may cause a variety of conditions, including age-related macular degeneration (AMD) and diabetic retinopathy (DR). these diseases. The gold standard treatment for posterior segment proliferative vascular disease utilizes anti-vascular endothelial growth factors' is also a common posterior segment disease and the most common and serious microvascular complication of diabetes. Considering the increasing prevalence of diabetes worldwide, DR remains the leading cause of preventable blindness, with one third of people with diabetes expected to develop Breakthrough insulin therapy effectively suppresses the progression of DR, the short half-life of insulin limits its clinical application. To prolong insulin release, Rong et al. developed a biphasic nanoparticle/hydrogel delivery system "ICNPH". A PLGA-PEG-PLGA thermowell was used to encapsulate insulin-loaded chitosan nanoparticles. When ICNPH was injected subconjunctivally in a diabetic mouse model, insulin was continuously released for 60 days. ICNPH group significantly reduced retinal cell apoptosis and his VEGF and glial fibrillary acidic protein (GFAP)

expression, resulting in neuroprotective effects on DR. Methylcellulose (MC) was added to disulfiram (DIS) nanoparticles to form an in-situ eye gel formulation (DIS-NPs/ISG). Several intraocular implants are commercially available or in clinical trials to treat severe conditions of the posterior segment, including macular degeneration. These include the non-biodegradable products Vitrasert, Retisert, Medidur, and Iluvien, as well as the biodegradable products Posurdex, Ozurdex, and Surodex. Most of these implants are filled with small amounts of medications such as fluocinolone acetonide, dexamethasone, and ganciclovir. There are currently no biological support implants available on the market, although some are in ganciclovir. There-VEGF therapy plays a central role in the pathogenesis of choroidal neovascularization and has revolutionized the treatment of diabetic retinopathy and AMD.

Thermogel for Diabetic Retinopathy (DR)

DR is a common posterior segment disease and the most common and serious microvascular complication of diabetes. As the prevalence of diabetes increases worldwide, DR remains the leading cause of preventable blindness, with one-third of people with diabetes expected to develop DR. Intensive diabetes treatment by controlling blood sugar levels and blood pressure can reduce the risk of development and progression of retinopathy. Although insulin therapy effectively suppresses the progression of DR, the short half-life of insulin limits its clinical application. To prolong insulin release, Rong et al. developed a PLGA-PEG-PLGA thermogel to encapsulate insulin-loaded chitosan nanoparticles. When CNPH was injected subconjunctivally in a diabetic mouse model, insulin was continuously released for 60 days. CNPH group significantly reduced retinal cell apoptosis and the expression of VEGF and glial fibrillary acidic protein (GFAP), resulting in neuroprotective effects on DR. Professor Nagai's group in Japan adopted a similar nanoparticle/hydrogel approach for the treatment of DR, adding methylcellulose (MC) to disulfiram (DIS) nanoparticles in Forman in situ eye gel formulations (DIS-NPs/ISG). This formulation was instilled into the right eye of a diabetic mouse model for one month, but no precipitate was detected. IS was converted to diethylthiocarbamate (DDC), and the latter was abundant in the right retina and inhibited the expression of inducible nitric oxide synthase (iNOS), suggesting that DIS-NP/ISG is an effective retinal agent. It was suggested that this drug delivery system could be used as DR.

Thermogel for age related Macular Degeneration (AMD)

This is a progressive chronic disease of the central retina that can lead to blindness in the later stages of the disease due to neovascular AMD ('wet') and geographic atrophy ('late dry'). Multiple intravitreal injections of anti-VEGF are the current treatment for "wet" macular degeneration, which inhibits the generation of new blood vessels and signaling for angiogenesis. These have been shown to significantly reduce "wet" AMD-related vision loss, motivating continued research into AMD treatment. A simple and functional studied due polymer consisting of pentaerythritol (PE), polyethylene glycol diacrylate (PEGDA), DL-lactic acid (LA), ϵ -caprolactone (CL), and PEG was synthesized to provide anti-VEGF, bevacizumab, or added aflibercept. AMD treatment. Several other PNIPAAm-based thermogels have been developed for intraocular antibody delivery. Egbu et al. designed an intraocular antibody delivery system composed of PNIPAAm, hyaluronic acid (HA), and PEGDA.

Controlled Delivery Potential treatment of p11 Peptide for angiogenic disorder of posterior segment

Retinopathy of prematurity (RP), age-related macular degeneration (AMD), and diabetic retinopathy (DR) are angiogenesis-related eye diseases that primarily occur between adolescence and old age, and are primarily prevalent worldwide. This is thought to be the cause of irreversible blindness. The main reasons for angiogenesis are hypoxia and oxidative stress, which further trigger a series of angiogenic events. Vascular endothelial growth factor (VEGF) is one of the key components in the normal angiogenic cascade. p11 is a cell-penetrating hexapeptide (HS-DVHK) that has an SDV sequence that specifically binds to $\alpha v \beta 3$ integrin instead of the RGD sequence, which is a common binding sequence of integrin motifs. p11 inhibits angiogenesis without side effects by blocking $\alpha v \beta 3$ integrin. However, the route of administration to the posterior segment of the eye remains a hurdle, making angiogenic eye diseases a major cause of blindness. Among various routes of drug administration, oral and systemic administration of antiangiogenic drugs/peptides are not suitable as they require large drug exposure and cause systemic side effects. Intravitreal injections are currently an FDA-approved treatment. This hydrogel is a cold-flowing sol that can be injected in combination with drugs and forms a non-flowing gel at body temperature, thus acting as a sustained drug delivery site in vivo and showing potential for ophthalmic applications.

Temperature Sensitive synthetic hydrogel

Temperature-sensitive hydrogels have been widely investigated as a system for slowly delivering therapeutic proteins to the fundus of the eye due to their rapid in situ gelation properties. After administration of the formulation, switching from room temperature to body temperature causes gelation. These systems are characterized by a phase transition at a specific temperature in aqueous solution, called "LCST (lower critical solution temperature) gelation. These polymers are most commonly used in the pharmaceutical field for the formulation of injectable hydrogels and are characterized

by a His LCST between room temperature and body temperature. Formulations based on this type of polymer are liquid at room temperature and rapidly gel at body temperature after administration, allowing them to be used as injectable delivery systems. Therapeutic agents can be easily loaded into these gels by dissolving/dispersing them in the hydrogel precursor solution. After cross-linking, the encapsulated drug is released in a controlled manner with kinetics depending on the size of the therapeutic agent, pore size of the hydrogel, and swelling/degradation, among others.

Thermosensitive Composite

NPs and microparticles (MPs) are colloidal systems that offer similar advantages to liposomes, as well as flexibility in the route of administration, tunable size, and a surface whose functionality can be responsive to external stimuli. MPs or NPs suspended in gel matrices (composite systems), generally composed of biodegradable polymers, have emerged as versatile platforms for ocular drug delivery applications, resulting in fewer side effects and thereby improving intraocular the frequency of injections may be reduced. Tan et al. [80] recently incorporated a nanostructured lipid carrier (NLC) into a hydrogel consisting of hydroxypropyl trimethylammonium chloride, chitosan, and β -glycerophosphate to form an NLC-loaded hydrogel carrier, an interesting thermosensitive in situ gel. We have developed a chemical formulation. Eye sustained release. While the thermo-responsive composites described above were designed for precorneal treatments, a number of formulations based on MP or NP incorporated into thermosensitive gels are described in the literature as useful injectable systems for cell and therapeutics intraocular delivery.

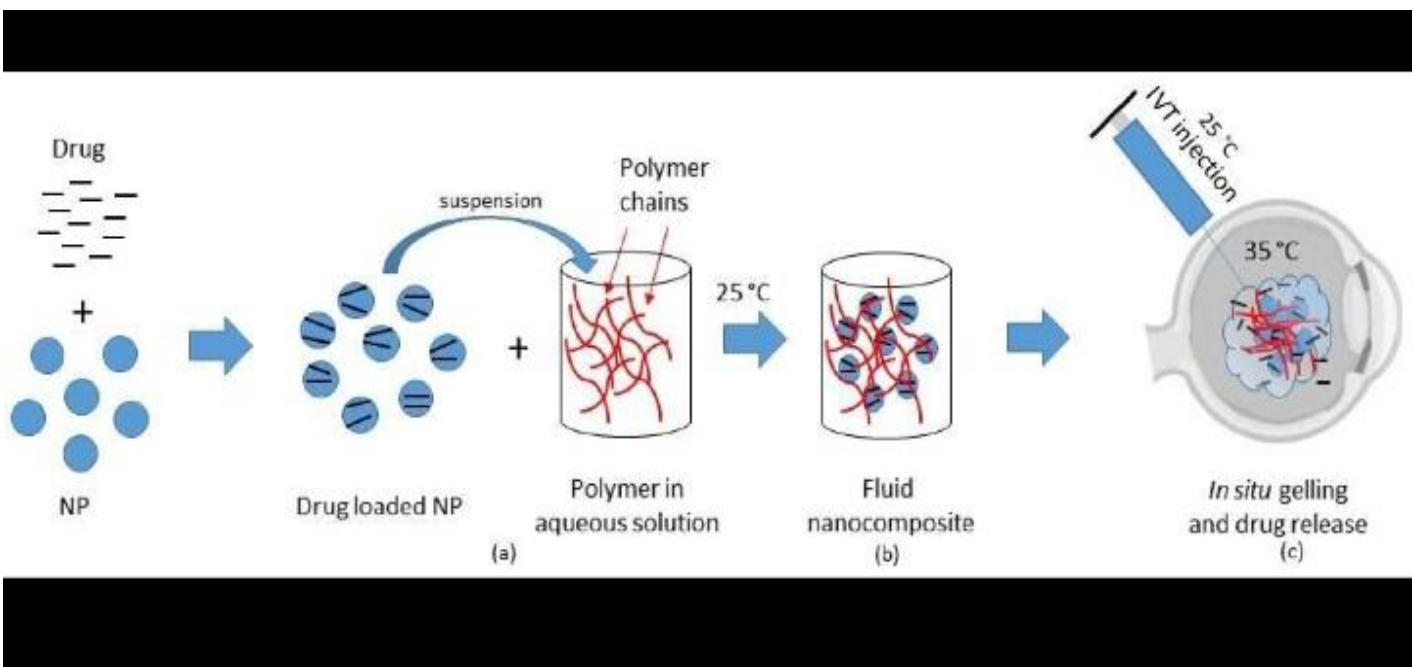


Figure: - 4 Possible scheme of preparation and Intravitreal injection of a thermosensitive Nano composite system: (a) Drug loaded NP are suspended in a polymeric solution at 25 °C. (b) Polymeric solution-suspended NP form a fluid injectable Nano composite system at 25 °C. (c) The fluid Nano composite system is injected in the vitreous at 25 °C; the temperature-induced phase transition occurs at 35 °C, resulting in in situ gel formation and sustained drug release.

Innovative technologies for posterior Segment

New drug delivery systems are currently being used by clinicians to maintain and prolong drug release to treat posterior segment diseases such as DR, AMD, DME, retinal vein occlusion (CRVO), and posterior uveitis. I by clinicians following section introduces the various intravitreal implants currently available in the clinic and undergoing clinical trials.

Durasert Drug-Delivery Technology System

The Durasert technology system “pSivida Corp., Watertown, MA” delivers medication at various predetermined times, depending on the design of the implant. Drug release can last from days to years. Durasert consists of a drug core and a surrounding polymer layer. Drug release is a function of the permeability of the polymer layer. Vitrasert (Bausch & Lomb) is the first intravitreal drug delivery system incorporating an antiviral drug (ganciclovir) for the treatment of cytomegalovirus retinitis. It uses the Durasert technology system, which releases the active ingredient for 6 to 8 months through a small opening in the insert (Chang and Dunn, 2005). Iluvien (fluocinolone acetonide intravitreal implant, Alimera Sciences, Inc.) is the latest intravitreal injection approved by the US FDA for the treatment of DME.A

multicenter randomized clinical trial showed that both low and high doses of Iluvian significantly improved visual acuity with fewer side effects. Iluvian is being evaluated in a Phase II clinical trial for efficacy in macular edema secondary to dry AMD (NCT00695318), wet AMD (NCT00605423), and RVO compared to treatment with Lucentis (ranibizumab) (NCT00770770). Masu.

Encapsulated Cell Technology

A new technology using encapsulated human RPE cells has been developed by Neurotech Pharmaceuticals. NT-501 (Renexus®) consists of an implantable polymer scaffold that encapsulates cells that are genetically modified to secrete ciliary neurotrophic factor (CNTF). These capsule-containing cells are composed of a semipermeable membrane surrounding a scaffold of polyethylene terephthalate strands, which protects the cells from the immune system while allowing the passage of nutrients and therapeutic molecules. A titanium loop is attached to the end of this capsule, which allows it to be fixed to the scleral wall through the site plane after surgical implantation. The device was originally developed to treat RP and dry AMD, but is also being considered for the treatment of patients with glaucoma and macular telangiectasia type 2. Studies have shown that NT-501 slows retinal degeneration and stabilizes reading speed in patients. Various biocompatible polymers such as collagen and hyaluronic acid hydrogels are used to form his ECT matrix. The implant's capsule is semipermeable, allowing proteins to diffuse across the membrane, but tenterhook immune cells are inhibited. TECT may be advantageous compared to other corticosteroid implants because it can secrete biologically active molecules for long periods of time and requires less frequent implant replacement. Kanzuri et al. demonstrated a genetically modified RPE capable of secreting soluble VEGF receptors to suppress VEGF activity in choroidal and retinal neovascularization. Therefore, ECT can be considered a safe, effective, and well-controlled platform for the treatment of ocular fundus diseases with retinal dysfunction.

I-vation Triamcinolone Acetonide Drug-Delivery Technology

I-vation TA (SurModics Inc.) is also an Intravitreal drug-delivery implant for triamcinolone acetonide (TA). I-vation is a titanium helical coil implant coated with TA in a Nonbiodegradable polymer. Preclinical experiments suggest that I-vation vivo up to 2 years. The TA was well tolerated the patients as indicated by a minimal rise in IOP. The I-vation TA treatment also aided the reduction of macular thickness from baseline, indicating alleviate

TABLE NO :1 Approved drugs and those in current clinical trials for treatment of posterior segment diseases.

Name and company	Drug delivery platform	Drug and excipients	Indications and ongoing trials	Status
Brimonidine (Allergan)	i.v.t. implant	Brimonidine (0.4 mg) with PLGA	Dry AMD with GA	Phase II
Cortitect®/NOVA63035 (Novagali Pharma)	i.v.t.	Dexamethasone emulsion (preservative and solvent-free)	DME	Phase I/II
Durasert™ (pSivida Corp)	i.v.t. implant	Latanoprost with EVA/PVA	Ocular hypertension and glaucoma	Phase I/II
I-vation® (Surmodics Inc)	Reservoir i.v.t. implant	TA (0.925 mg) with PMMA/EVA	DME	Phase IIb
IBI-20089 (Icon Biosciences Inc)	i.v.t.	TA (6.0 mg or 13.8 mg) and benzyl benzoate with lucentis (0.5 mg)	AMD CNV	Phase I Phase II
Iluvien™ (Alimera Sciences, Inc.)	25-gauge i.v.t. implant	FA (0.19 mg) with polyimide/PVA	DME AMD with GA Posterior uveitis	Approved Phase II Phase III
NT-501/Renexus (Neurotech Pharma)	i.v.t. implant	CNTF with PET and ARPE-19 cells	Glaucoma RP	Phase I
NT-503 (Neurotech Pharma)	i.v.t. implant i.v.t. injection	Anti-VEGF receptor protein	Recurrent CNV with wet AMD	Phase I Phase II
NT-506 (Neurotech Pharma)	i.v.t. implant	Anti-PDGF/Anti-VEGF	Wet AMD	Preclinical
Ozurdex® (Allergan)	i.v.t. implant	Dexamethasone (0.7 mg) with PLGA	DME, CRVO, uveitis	Approved
Posurdex (Allergan)	i.v.t. implant	Dexamethasone	Posterior uveitis DME	Phase III Phase III
Retisert® (Bausch & Lomb)	Reservoir i.v.t. implant	FA (0.59 mg) with silicone/PVA	Non-infectious uveitis	Approved
Vitrasert® (pSivida Corp)	Reservoir i.v.t. implant	Ganciclovir with EVA/ PVA	CMV retinitis	Approved

Nanomedicine

Nanoparticles (NPs) are ideal for ocular drug delivery due to their nanometer-controllable size and ability to protect transported active molecules from degradation and enable targeted, controlled release. It has characteristics. Furthermore, NP surfaces have higher specificity and higher mucoadhesive properties due to higher interfacial availability for hydrogen and ionic bonding or hydrophobic interactions with mucus surfaces compared to larger bulk polymers. Recently, submicron liposomes have shown potential for use in the treatment of posterior segment diseases in the form of eye drops as a topical drug delivery system. Nanocarriers have the potential to overcome ocular barriers and deliver drugs to targeted sites. Nanomedicine is classified into polymer drug conjugates and nanoparticle systems. Various nanocarrier drug delivery systems include microemulsions, nano emulsions, nanosuspensions, dendrimers, niosome, nano micelles, nano wafers, liposomes, discums, cubosomes, polymer nanoparticles, polymer drug conjugates, solid lipid nanoparticles, Includes nanostructured lipid carriers, nanocarrier-loaded gel systems, etc.

Applications of Hydrogel

Subconjunctival injection

Subconjunctival injection is safe and easily achieves sustained release of drug to the ocular surface. Ron et al. A dual controlled release system was prepared by adding insulin-loaded chitosan nanoparticles (ICNs) to polylactic acid-polyethylene glycol-poly(lactic acid) hydrogels (PLGA-PEG-PLGA). When the nanoparticles were injected subconjunctival, there was no obvious damage to retinal function, structure, or neurons. This proved that the hydrogel can be safely used for subconjunctival injection. Subconjunctival injection of hydrogels will be the focus of ocular administration studies in the near future.

Corneal contact lenses

Corneal contact lenses are a type of ocular surface repair device, and are currently mainly used for vision correction and as a type of drug filling treatment for ocular surface diseases. In terms of optical properties, PHEMA hydrogels have excellent transparency. Transmittance and refractive index suitable for ophthalmological applications. Tests using a refractometer showed that the refractive index of pure PHEMA hydrogel is approximately 1.410, similar to the refractive index of the human natural lens. This value can be enhanced by copolymerization with other chemicals such as titanium (IV) oxide (TiO₂) for intraocular lens implantation applications.

Vitreous injection

When administered through the ocular surface, it is difficult to deliver drugs to the intraocular surface. Therefore, intravitreal injection is the most common method of drug administration in the clinic. Materials with good biocompatibility, such as hydrogels, have been described as vehicles for injection into the vitreous. Yu et al. investigated an injectable chemically cross-linked hydrogel for controlled intravitreal release of bevacizumab. They found that a clear gel was observed after intravitreal injection, and there was no ocular hemorrhage, retinal detachment, inflammation, or other pathological changes.

Promoting repair patch

Although most corneal surgeries use nylon sutures, many corneal complications such as inflammation and corneal neovascularization occur. Therefore, nylon sutures should be replaced with biocompatible mesh. 82,83 Hydrogels can adapt to dynamic soft tissues and withstand normal movements, making them excellent carriers for adhesive plasters. The adhesive properties of the hydrogel patch were recently tested on implanted porcine eyes and it was found that the patch was able to firmly adhere to the corneal surface. The extent of lesions that can be closed by the hydrogel patch technique was evaluated using three different types of open lesions: large linear lesions, cruciate ligament lesions, and tissue-deficient lesions. It was demonstrated that the patch could cover the entire width of the lesion and that the hydrogel conformed well to the edges of the lesion and provided a smooth surface.

Micro needle

Microneedles can also provide sustained drug release, making them suitable for a variety of applications 80. In recent years, with the advent of hydrogels, hydrogel-forming microneedles have been widely reported. Hydrogel-forming microneedles swell when inserted into the skin, providing a hydrophilic effect. Compared with other types of microneedles, hydrogel-forming microneedles have excellent drug loading ability and good biocompatibility, and can be molded into various shapes⁸¹. Currently, hydrogel-forming microneedles have not been widely reported in ophthalmological research, which represents a positive sign. Future prospects are shown.

Medical devices

Some injectable hydrogels can be utilized as medical devices. For example, the nanocomposite of hydrophilized silica nanoparticles in hydrophobically modified poly (ethylene glycol) forms an in-situ gelling hydrogel which was developed as an injectable accommodative intraocular lens.

Summary

In this review, we summarize the recent progress of hydrogel research for posterior segment diseases. Ocular drug delivery using injectable hydrogels involves the administration of therapeutic agents directly into the eye in a gel form. This method offers controlled release, improving drug bioavailability and reducing the need for frequent applications. Injectable hydrogels provide a versatile platform for sustained drug delivery, enhancing treatment efficacy for various posterior segment diseases. Thermogels, or thermo-responsive hydrogels, are a subclass of the supramolecular hydrogels that gelate via hydrophobic interactions. These are still amongst the most effective and useful in situ formed hydrogels due to the universality of tapping on physiological temperatures for ophthalmic application.

Conclusion

Ocular drug delivery has been a major challenge due to the unique anatomy and physiology of the eye. Treatment for Posterior segment disease still remains a huge task for formulation scientist. Ocular drug delivery using injectable hydrogel involves the administration of therapeutic agents directly into the eye in the form of gel. Ocular drug delivery using injectable hydrogel involves the administration of therapeutic agents directly into the eye this method it provides control release. improved bioavailability and reducing the need for frequent application. The use of injectable hydrogel for ocular drug delivery to the posterior segment shows promise in improving therapeutic outcomes. Enhanced drug retention, sustained release, and targeted delivery contribute to better treatment efficacy. however further research is needed to address challenges. such as long-term safety, biocompatibility. Hydrogels effortlessly overcome the limits of traditional dosage forms such as eye drops, ointments, Lenses etc., In spite of this hurdles, injectable hydrogel represent

beneficial path for ocular drug delivery. Along with this, thermogels provide a promising path for Ocular drug delivery such as providing controlled and sustained release of drugs. Thermogels, or thermo-responsive hydrogels, are a subclass of the supramolecular hydrogels that gelate via hydrophobic interactions. This are still amongst the most effective and useful in situ formed hydrogels due to the universality of tapping on physiological temperatures for ophthalmic application.

REFERENCES:

1. D.S., Kurade, Prof. D.G. Joshi, Mrs. Anita. A Review on Ocular Drug Delivery with New Trends (2015). Volume 3, Issue 11. 629.
2. S. Ahmed, · M.M. Amin, S. Sayed, Ocular Drug Delivery: A Comprehensive Review. AAPS Pharm SciTech (2023) 24:66
3. T. M. Wankhede¹, A. M. Wankhede, Ocular Drug Delivery System: Review. April 2021 Vol.:21, Issue:1 ,313-336
4. A. Subrizi¹, Eva M. del Amo, V. Korzhikov-Vlakh, T. Tennikova, M. Ruponen, and A. Urtti¹, Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties.1446-1457.
5. S. Li¹, L. Chen and Y. Fu¹, Nanotechnology-based ocular drug delivery systems: recent advances and future prospects. Li et al. Journal of Nanobiotechnology July, 2023, Journal of Nanotechnology. 21(1):232 1-39
6. K. Zhang, K. Xue, and X. Jun Loh, Thermo-Responsive Hydrogels: From Recent Progress to Biomedical Applications, Gels 2021, 7, 77. -1-17
7. H. Omidian and S. D. Chowdhury, Advancements and Applications of Injectable Hydrogel Composites in Biomedical Research and Therapy. Gels 2023, 9, 533. -1-37
8. R. Gaudana J. Jwala¹, Sai H. S. Boddu¹, and A. K. Mitra^{1,2} Recent Perspectives in Ocular Drug Delivery Pharm Res. 2009 May; 26(5): 1197–1216.
9. V. Ratnam G, Madhavi, Rajesh P, ocular drug delivery: an update review, IJPBS |Volume 1| Issue 4 |OCT-DEC |2011|437-446-, 438
10. Q. Wang, Y. Zhang^b, Y. Mab, M. Wang, G. Pana, Nano-crosslinked dynamic hydrogels for biomedical applications, Master Today Bio.2023 Jun ;20:100640 1-31.
11. Q. Wang, Z. Zuo· C. K. C. Cheung, S.S. Y. Leung Update on thermosensitive hydrogel for nasal, ocular and cutaneous delivery. International journal of pharmaceutics, 2019 Mar25:559:86-101
12. K. Wang¹ and Z. Han, Injectable hydrogels for ophthalmic applications, J Control Release. 2017 Dec28; 268:212-224.
13. S. Almawash, S. K. Osman, G. Mustafa and M.A. ElHamd^{1,3}, Current and Future Prospective of Injectable Hydrogels—Design Challenges and Limitations, Pharmaceuticals 2022 18,15(3)371. 1-44.
14. D. J. Overstreet, D. Dutta, Sarah E. Stabenfeldt, Brent L. Vernon, Injectable hydrogel, Journal of Polymer Science part B Polymer Physics science/Volume 50, Issue13.1-22.
15. K. Wang and Z. Han, Injectable hydrogels for ophthalmic applications, J Control Release. 2017 December 28; 268: 212–224. 2017.10.031.
16. K. Wang, Cross-Linked Hydrogel for Pharmaceutical Applications: A Review, Adv Pharm Bull, 2017, 7(4), 515-530 - 520.
17. P. Bhattacharjee, and M. Ahearne, Significance of Crosslinking Approaches in the Development of Next Generation Hydrogels for Corneal Tissue Engineering, Pharmaceuticals 2021, 13, 319. 3-23
18. Fernando J. Cabrera¹, Daniel C. Wang, K. Reddy, G. Acharya, and Crystal S. Shin, Challenges and opportunities for drug delivery to the posterior of the eye, Drug Discovery Today.2019 Aug,24(8);1679-16684.
19. V. Ow | X. J. Loh Recent developments of temperature-responsive polymers for ophthalmic application, Journal of Polymer science /Volume 60, Issue 9 – 1435-1437.
20. S. Sapino, D. Chirio, E. Peira, V. Brunella, S. A. Jadhav. E.A. Rubio ³, G. Chindamo and M. Gallarate, Ocular Drug Delivery: A Special Focus on the Thermosensitive Approach, Nanomaterials 2019, 9, 884; 1-19
21. B. C. Ilochonwua. A. Urttib, c, W. E. Henninka, T. Vermondena, Intravitreal hydrogels for sustained release of therapeutic proteins, Volume 326,10 October 2020-419-441.
22. V. Gote, S. Sikder, J. Sicotte, and D. Pal, Ocular Drug Delivery: Present Innovations and Future Challenges, J Pharmacology Exp Ther 370:602–624, September 2019.
23. A. Gabai, M. Zeppieri, L. Finocchio, Gate, Innovative Strategies for Drug Delivery to the Ocular Posterior Segment, Pharmaceuticals 2023, 15, 1862. 1-38
24. C. S Amrutkar, S. B Patil, Nanocarriers for ocular drug delivery: Recent advances and future opportunities, 2023 Indian Journal of Ophthalmology.2023 Jun;71(6):2355-2366.
25. S, Awwad, A. Ahmed, G. Sharma, J.S. Heng Principles of Pharmacology in the Eye, September 2017.British Journal of Pharmacology.174(23).

26. L. Zheng, Y. Han, of. Zhu, X.J. Loh, Z.Li, and C. Li, Recent Advances in Ocular Therapy by Hydrogel Biomaterials, Vol. 1 (2023) 2230002 ,20.
27. K. Saptaji, N. Riza, S. Widianingrum, V. K. Mulia, I. Setiawan, Poly (2-Hydroxyethyl Methacrylate) Hydrogels for Contact Lens Applications–A Review, Makara Journal of Science Makara Journal of Science Volume 25 Issue 3 September. (2021) 145-154.
28. A. Mellati, and J. Akhtari, Injectable Hydrogels: A Review of Injectability Mechanisms and Biomedical Applications, Research in Molecular Medicine (RMM), vol. 6 (2018), Issue No. 4, 1-20.