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Review Article

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AN OVERVIEW: IN-SITU GEL AND MODERN OCULAR DRUG DELIVERY SYSTEM

Parag G. Nakhare*[1], Omkar Tipugade[2], Shobharaj Malavi[3] and Sadanand Khair[2]

[1]Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Karad-415111, MS, India.
[2]Department of Pharmaceutics, Genesis Institute of Pharmacy, Radhanagari-416212, MS, India.
[3]Department of Pharmaceutics, Government College of Pharmacy, Karad-415110, MS, India.

***Corresponding Author: Parag G. Nakhare**

Department of Pharmaceutical, Shree Sant Krupa College of Pharmacy, Ghogaon, Karad, Maharashtra.

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ABSTRACT

Ocular Drug Delivery has been a significant testing and intriguing field for the pharmaceutical researcher because of novel life structures and physiology of eye. The poor bioavailability of conventional ophthalmic formulations is due to rapid pre-corneal drug loss (through dilution and drain from the eye). The matter will be overcome by in situ forming ophthalmic drug delivery system ready from chemical compound (polymer) that exhibit reversible liquid-gel phase transition. In situ gels are the liquid preparations which upon instillation undergoes phase transition in cul-de-sac of the eye to make a viscous gel and this happens because of the environmental changes within the eye (i.e. This novel drug delivery system promotes the significantly ease and convenience of administration, retrieval of correct dose as well as to prolong residence time of drug in contact with mucosa. This review is to specify the essential anatomy and physiology of human eye, numerous approaches used for formulation of in-situ gels and polymers utilized in the formulation of in situ gels.

KEYWORDS: Ocular drug delivery, In-situ gel, Biodegradable polymer, PH sensitive, Temperature sensitive, Ion sensitive.

INTRODUCTION

Eyes are vital sensory organs in the human body, which convert light to an electrical signal that later will be interpreted by brain.[1] Broadly, the human eye is split into two segments that are anterior and posterior segments[2] (Fig. 1). It will prohibit the entry of any exogenous substance attributable to its anatomical-physiological structure and defence mechanisms.[1] It gets suffer from different diseases like glaucoma, dry eye syndrome, trachoma, keratitis, and conjunctivitis etc.[3] Most ocular diseases are treated by topical drug application in the form of solutions, suspensions and ointment.[4] The conventional drug delivery such as suspension, ointment, solution show some drawbacks like increase pre-corneal drainage, blurred vision, low bioavailability low residence time. The absorption of medication within the eye is severely restricted by some protecting mechanisms that make sure the correct functioning of the eye, and by different concomitant factors like, drainage of the instilled solutions, lacrimation and tear turnover, metabolism, tear evaporation, non-productive absorption/adsorption, limited corneal area and poor corneal permeability, binding by the lachrymal proteins[5] and complex penetration barriers (Corneal Barrier, Blood Aqueous Barrier (BAB), and Blood Retinal Barrier (BRB))[2] (Fig. 2). In order to surpass the drawbacks associated with the conventional ophthalmic formulations, several makes an attempt are created towards the development of stable sustained release in situ gel.[6] In situ gel system is developed as liquid preparation appropriate to be instilled into eyes that upon exposure to the physiologic environment changes to gel results in in-situ gel, thus increasing the pre-corneal residence time of the delivery system, and enhances the ocular bioavailability of the drug.[7] Both natural and synthetic polymers can be utilized for the production of in situ gels.[8] In situ forming gels are formulations, applied as solutions, sols, or Suspensions, that undergo gelation after instillation due to physicochemical, changes characteristic to the eye. The objective of this review is to explain the varied temperature, pH, and ion induced, in situ-forming polymeric systems used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability.[9]

ANATOMY OF THE EYE

The human eye is split into two segments i.e. anterior segment which involves the cornea, conjunctiva, iris, pupil, ciliary body, anterior chamber, aqueous humour, lens and trabecular meshwork and also the posterior segment includes vitreous humour, sclera, retina, choroid, macula and optic nerve.[10]

The outermost transparent membrane of the eye is cornea such are the corneal epithelium, bowman's membrane,

stroma, descemet's membrane, and endothelium. The anterior segment may be a fluid of the eye which contains the source of nutrition to the crystalline lens and cornea. The iris sphincter and dilator muscles are help full to adjust the pupil size which regulates the amount of light entering to the eye.[11] 80% of the eye is filled with a clear gel known as vitreous. Light passes through the pupil and also the lens then it will reaches back of the eye. The retina transforms light into electrical impulses. Behind the eye, the optic nerve conveys these impulses to the brain. The macula could be a tiny extra-sensitive space which is present in retina that gives central vision.[12]

BARRIERS FOR OCULAR DELIVERY

Drug Loss from the Ocular Surface

After instillation the flow of lacrimal fluid expels instilled compounds from the surface of the eye. Routes of drug kinetics discuss with following processes:

1) Transcorneal permeation into the anterior chamber from lachrymal fluid.
2) Non-corneal drug permeation through the conjunctiva and sclera into the anterior uvea.
3) Drug distribution from the blood stream via blood-aqueous barrier into the anterior chamber.
4) Elimination of drug from the anterior chamber to the aqueous humour turnover to the trabecular meshwork and Sclemm's canal.
5) Drug removal from the aqueous humor into the systemic circulation across the blood-aqueous barrier.
6) Drug distribution from the blood into the posterior eye across the blood-retina barrier and intravitreal drug administration.
7) Drug elimination from the vitreous via posterior route across the blood-retina barrier.
8) Drug elimination from the vitreous via anterior route to the posterior chamber.[10,13]

Though the lacrimal turnover rate is approximately 1 µl/min the excess quantity of the instilled fluid goes to the nasolacrimal duct rapidly in a more than one minutes. Another reason of non-productive drug removal is its systemic absorption in preference to ocular absorption. Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.[13]

Lacrimal Fluid-Eye Barriers

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions that restriction the paracellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs.[5] Generally, the conjunctiva is leakier epithelium than the cornea and its surface region is also nearly 20 times larger than that of the cornea.[14] Absorption of the drug across the bulbar conjunctiva has gained increasing attention recently, since conjunctiva is fairly permeable to the hydrophilic and large molecules. Therefore, for larger bio-organic compounds together with proteins and peptides it is able to serve as a route of absorption.[10]

Blood- Ocular Barriers

The eye is shielded from the xenobiotic within the blood stream by blood-ocular barriers. These barriers have two types: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells within the uvea it is the middle layer of the eye beneath the sclera. It consists of the iris, ciliary body and choroid. This barrier prevents the get right of entry to of hydrophilic drugs and plasma albumin into the aqueous humor.[5] The posterior barrier between blood stream and eye is consisting of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries. Inflammation might also interrupt the integrity of this barrier causing the unlimited drug delivery to the anterior chamber. In fact the permeability of this barrier is poorly categorized. Unlike retinal capillaries the vasculature of the choroid has wide blood flow and leaky walls.[10] Drugs easily benefit get entry to the choroidal extravascular space however after that distribution into the retina is limited via the RPE and retinal endothelia. Despite its high blood flow the choroidal blood flow establishes only a minor fraction of the entire blood flow in the body. Unlike blood brain barrier the blood-eye barriers have not been taken into consideration in phrases of drug transporter and metabolic enzyme expression.[13]

Fate of Formulation Administered Through Eye

The overall method of absorption into the eye from the precorneal space (dose site) following topical ocular administration is sort of complicated. The classical series of occasions involves drug instillation, dilution in tear fluid, diffusion via mucin layer, corneal penetration (epithelium, stroma, endothelium), and transfer from cornea to aqueous humor. Following absorption, drug distributes to the site of action (e.g., iris-ciliary body).[6] Parallel absorption via the conjunctiva/sclera provides an extra pathway to eye tissues but, for most drugs, is minor compared with corneal absorption. Also, non-productive, competing, and parallel pathways (e.g., nasolacrimal drainage or systemic absorption via the conjunctiva) work to carry drug away from the eye and limit the time allowed for the absorption process. Moreover, in few species, such as the rabbit, non-productive absorption into the nictitating membrane can occur. Figure 3 presents a summary of these pre-corneal activities, with a relatively simplified view of the kinetics in the cornea, aqueous humor, and anterior segment.[5]

IN SITU GELLING SYSTEM

The 'in situ gel' system has emerged as considered one of the best novel drug delivery systems, the in situ gelling system helps for the sustained and controlled release of the drugs, improved patient compliance and comfort by its special characteristic feature of 'Sol to Gel' transition.[16] This in situ gelling system is when exposed

to physiological circumtance will shift to a gel phase.[17] Three methods have been employed to motive phase transition at the surface: change in temperature, pH, and electrolyte composition.[4] This novel concept of producing in situ gel was recommended for the primary time in the early 1980s. Gelation happens via the cross-linking of polymer chains that can be executed via covalent bond formation (chemical cross-linking) or non-covalent bond formation (physical cross-linking). In situ gel-forming systems can be described as low viscosity solutions that go through phase transition in the conjunctival cul-de-sac to form viscoelastic gels due to conformational modifications of polymers in response to the physiological environment.[6] The rate of in situ gel formation is important because between instillation in the eye and before a strong gel is formed; the solution or weak gel is produced by the fluid mechanism of the eye. Both natural and synthetic polymers may be used for the manufacturing of in situ gels.[18]

IMPORTANCE OF IN SITU GELLING SYSTEM[8,16]

- ✓ The primary significance is the opportunities of administrating accurate & reproducible quantities as compared to already formed gel.
- ✓ In-situ forming polymeric delivery system such as ease of administration & decreased frequency of administration advanced patient compliance & comfort.
- ✓ It helps for the controlled and sustained release of the drug by its special 'sol Gel transition.
- ✓ Low dose of the drug is required and there"ll be no drug accumulation and no side effects.
- ✓ The bioavailability of the drug will be more.
- ✓ There could be increased residence time of the drug because of gel formation.
- ✓ The in situ gel system decreases wastage of the drug.
- ✓ Liquid dosage form that can sustain drug release & continue to be in contact with cornea of eye for extended period of time is ideal.
- ✓ Reduced systemic absorption of drug drained through the nasolacrimal duct may bring about a few undesirable side effects.

ADVANTAGES[8,16,19]

- ✓ Ease of administration.
- ✓ Reduced frequency of administration further.
- ✓ Improved patient compliance and comfort.
- ✓ Can be administered to subconscious patients.
- ✓ Drug gets released in a sustained and controlled manner.
- ✓ Natural polymers have inherent properties of biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities.
- ✓ Synthetic polymers typically have well-described structures that can be modified to yield tailorable degradability and functionality.
- ✓ In situ gels can also be engineered to exhibit bio adhesiveness to facilitate drug targeting, in particular via mucus membranes, for non-invasive drug administration.
- ✓ In situ gels offer an important "stealth" characteristic in vivo, because of their hydrophilicity which increases the in vivo circulation time of the delivery tool by way of evading the host immune response and decreasing phagocytic activities.

DISADVANTAGES[20]

- ✓ It is more susceptible due to storage problems due to chemical degradation.
- ✓ It requires excessive level of fluids.
- ✓ It leads to degradation due to storage problems.

LIMITATIONS[8]

- ✓ The quantity and homogeneity of drug loading into hydrogels may be limited, mainly for hydrophobic drugs.
- ✓ Only drugs with small dose requirement can be given. · Lower mechanical strength, may result into premature dissolution or glide away of the hydrogel from a targeted local site.
- ✓ The high water content and enormous pore size of most hydrogels often result in relatively rapid drug release.
- ✓ Simple application is questionable sometimes as some hydrogels are not sufficiently deformable, thus injectable route may not be possible.
- ✓ Eating and drinking may become restricted up to few hours.

MECHANISM OF IN SITU GEL

In situ formation based on physical mechanism:

Swelling

In situ formation can also arise when material absorbs water from surrounding environment and make bigger to arise desired space.[8] One such substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some Bio adhesive properties and may be degraded in vivo by way of enzymatic action.[21]

Diffusion

Diffusion is a type of physical approach that is utilized in in-situ gel formation. In this approach, solvent gets diffused out from the polymer solution into surrounding tissues which outcomes inside the formation of precipitate or solidification of polymer matrix. The most commonly used polymer in diffusion approach of formation of in-situ gelling system is N-methyl pyrrolidone (NMP).[20]

In situ formation based on chemical reactions

A chemical reaction that cosequences in situ gelation may contain precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

Ionic crosslinking

Polymers may undergo phase transition in presence of different ions. Some of the polysaccharides fall under the

category of ion-sensitive ones.[22] While k-carrageenan forms rigid, brittle gels in reply of small amount of K+, i-carrageenan forms elastic gels mainly inside the presence of Ca2+. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling within the presence of mono- and divalent cations, such as Ca2+, Mg2+, K+ and Na+. Gelation of the low-methoxy pectins may be as a result of divalent cations, particullarly Ca2+. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations.[17,8]
e.g. Ca2+ due to the interaction with guluronic acid block in alginate chains.[22]

Enzymatic cross-linking
Enzymatic cross linking is the most suitable technique used in formation of in situ gelling system. In this technique, gel is formed by way of cross linking with the enzymes which are present in body fluids. In situ formation induce by natural enzymes and that are not been investigated widely but appear to have some advantages over chemical and photochemical methods.[16] For example, an enzymatic procedure handles efficacy under physiologic conditions and no need for possibly destructive chemicals consisting of monomers and initiators. Hydrogels are utilized in intelligent stimuli-responsive delivery systems which will release insulin have been investigated. Modify the amount of enzyme also maintain an appropriate mechanism for controlling the rate of gel formation, which confess the mixtures to be injected before gel formation.[5]

Photo-polymerization
Photo polymerizable systems when added to the preffered site through injection get image cured in-situ with the assist of fiber optic cables and then release the drug for extended period of time. A photo polymerization, biodegradable hydro gels as a tissue contacting material and controlled release carrier.[23]

VARIOUS APPROACHES OF *IN SITU* GELATION

PH triggered in situ gelation
All the pH-sensitive polymers comprise pendant acidic or basic groups that either receive or release protons in response to adjustments in environmental pH. The polymers with a large number of ionizable groups are referred to as polyelectrolytes. Swelling of hydrogel increases because the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer includes weakly basic (cationic) groups.[10] Polyacrylic acid (Carbopol 940) is used as the gelling agent in combination with hydroxypropylmethylcellulose (Methocel E50LV) which acted as a viscosity improving agent. The formulation with pH-triggered in-situ gel is therapeutically efficacious, stable, non-irritant and provided sustained release of the drug for longer period of time than conventional eye drops. Another example cellulose acetate phthalate (CAP) is a polymer undergoing coagulation while the unique pH of the solution (4.5) is raised to 7.4 by the tear fluid.[24]

Temperature triggered in situ gel
The system is designed to use Poloxamer as a vehicle for ophthalmic drug delivery using insitu gel formation property. The gelation temperature of graft copolymers may be decided via measuring the temperature at which immobility of the meniscus in each solution become first noted.[25] The bioadhesive and thermally gelling of these graft copolymers antcipated to be an excellent drug carrier for the prolonged delivery to surface of the eye. Other example of Poloxamer 407 (apolyoxyethylene polyoxypropylene block copolymer) is a polymer with a solution viscosity that increases when its temperature is raised to the eye temperature.[18]

Ion activated *in situ* gelation
In this method, gelling of the solution instilled is caused by change in the ionic strength. It is thought that the rate of gelation depend on the osmotic gradient throughout the surface of the gel. The aqueous polymer solution forms a clear gel within the presence of the mono or divalent cations usually found within the tear fluids.[8] The electrolyte of the tear fluid and especially Na+, Ca2+ and Mg2+ cations are especially proper to initiate gelation of the polymer when instilled as a liquid solution in the conjunctival cul-de-sac. The polymer which indicates osmotically induced gelation is Gelrite or Gellan gum, Hyaluronic acid and Alginates etc.[13]

POLYMERS USED AS IN SITU GELLING AGENTS[5,10,18]

A polymer used in in situ gels should have following characteristics

- It should be biocompatible.
- It is capable of adhering to the mucus membrane.
- It should have pseudo plastic behaviour.
- Good tolerance and optical behaviour of polymer.
- It should influence the tear behaviour.
- The polymer must be capable of decrease the viscosity with increasing shear rate there by offering reduced viscosity during blinking & stability of the tear film during fixation.

EVALUATION OF IN SITU OPHTHALMIC GEL

Physical Parameter
Physical parameters to be tested for in-situ gel solution are gelling capacity, clarity, pH and drug content estimation.[25]

Gelling Capacity Test
The gelling capacity of the prepared formulation is determined by setting a drop of the formulation in a vial containing 2.0 ml of freshly prepared simulated tear fluid and visually observe.[24,18]

Rheological studies
The viscosity measurements may be calculated via the use of Brookfield viscometer, cone and plate viscometer.

The *in-situ* gel formulation was placed in sampler tube. The formulation before gelling should have viscosity from 5 to 1000 mpas. After ion gel activation in the eyes it will have viscosity of approximately 50-50,000 mpas. The samples are analysed each at room temperature at 25°c and thermo stated at 37°c ± 0.5°c via a circulating bath connected to viscometer adaptor prior to each measurement.[24,25]

Viscosity

Viscosity of the instilled formulation is an important factor in determining residence time of drug in the eye. The solutions had been allowed to gel within the STF after which the viscosity determinations were accomplished by using Brooke field viscometer, angular velocity ran from 10-100 rpm. Viscosity of the formulations increased with increase in polymer concentration. The hierarchy of shear rate was reversed and average of two readings was used to calculate viscosity.[10,33]

In vitro release studies

In vitro drug release study is performed through using Franz diffusion cell. In receptor compartment freshly prepared ATF is placed. Dialysis membrane is positioned (placed) in between receptor and donor compartments. Whole assembly is kept on the thermostatically controlled magnetic stirrer to simulate in vivo conditions and temperature of medium is maintained at 37oC ± 0.5oC. Medium is continuously stirred at 20 rpm. 1ml of formulation is placed in donor compartment. Sample (0.5ml) is withdrawn at predetermined time interval and same is replaced by ATF. Samples are analysed either on UV spectrophotometer or HPLC.[3]

Texture Analysis

The consistency, firmness and cohesiveness of *in situ* gel are assessed by the usage of texture profile analyser which in particular shows the gel strength and easiness in administration *in vivo*. The higher value of adhesiveness of gel needed to maintain an intimate contact with mucus surface.[25,7]

Isotonicity evaluation

Isotonicity is essential characteristics of the ophthalmic preparation. Isotonicity must be maintained to prevent tissue damage or irritation of eyes. All ophthalmic preparations are subjected to isotonicity testing, since they exhibit proper release characteristics and gelling capacity and the requisite viscosity. Formulation is mixed with few drops of blood and observed under microscope at 45x magnification and compared with standard marketed ophthalmic preparation.[17,25]

Drug-polymer interaction study and thermal analysis

Interaction study should be performed with Fourier Transform Infra-Red (FTIR) spectroscopy. During gelation process the nature of the interacting forces can be evaluated using the technique by employing KBr pellet method. Thermo gravimetric Analysis (TGA) can be conducted for in situ forming polymeric system to quantitate the proportion of water in hydrogel. Differential Scanning calorimetry (DSC) conducted to observe if there are any changes in thermo grams as compared with pure active ingredients used for gelation.[7,18]

Antibacterial activity

The microbiological growth of bacteria is measured by concentration of antibiotics and this has to be in comparision with that produced by known concentration of standard preparation of antibiotics. To carry out microbiological assay serial dilution method is employed.[25]

Sterility testing

Sterility testing was intended for detecting the presence of viable form of microorganisms and carried out for aerobic/anaerobic bacteria and fungi by using fluid thioglycolate medium and soybean-casein digest medium, respectively as per the Indian Pharmacopoeia 1996. Both the media had been observed each day for the presence or absence of turbidity and compared with a positive and negative control.[34]

Ocular irritancy test

The Draize irritancy test should design for the ocular irritation potential of the ophthalmic product prior to marketing. According to the Draize test, the amount of substance applied to the eye is generally 100µl placed into the lower cul-de-sac with observation of the various criteria made at a designed required time interval of 1hr, 24hrs, 48 hrs, 72hrs, and 1week after administration. Three rabbits (male) weighing 1.5 to 2kg are used for the study. The sterile formulation is instilled twice a day for a period of seven days, and a cross-over study is carried out (a three day washing duration with saline was carried out before the cross-over study). Rabbits are located periodically for redness, swelling, watering of the eye.[24,29]

Accelerated stability studies

Formulations are placed in ambient colour vials and sealed with aluminium foil for a short term accelerated stability have a look at 40±2 °C and 75±5% RH as per International Conference on Harmonization (ICH) states Guidelines. Samples are analysed every month for clarity, pH, gelling capacity, drug content, rheological evaluation, and in vitro dissolution.[30]

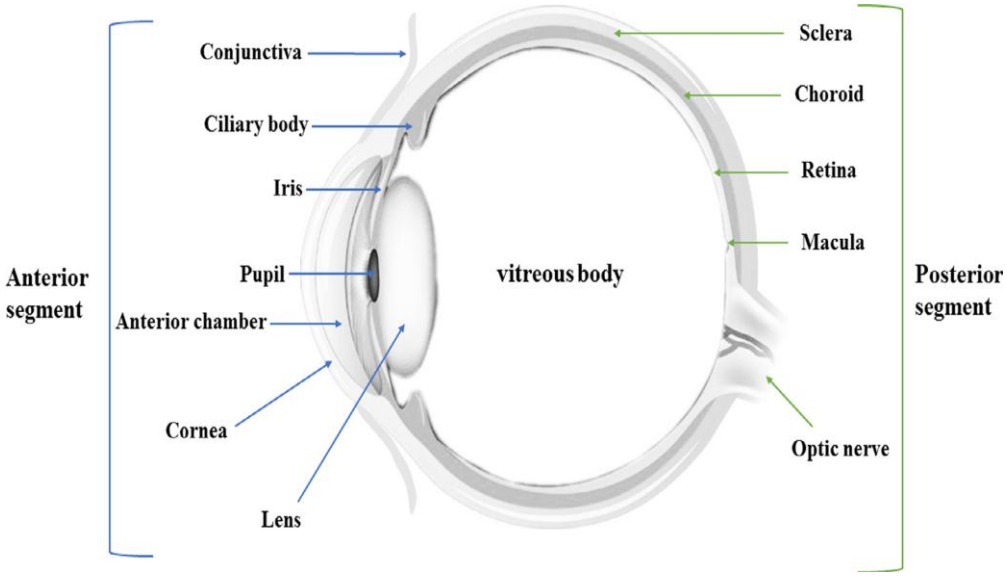

Figure No 1: The anatomy of ocular system: the anterior section involves conjunctiva, ciliary body, iris, pupil, anterior chamber, cornea and lens; the posterior section consists of choroid, retina, sclera, optic nerve and macula.

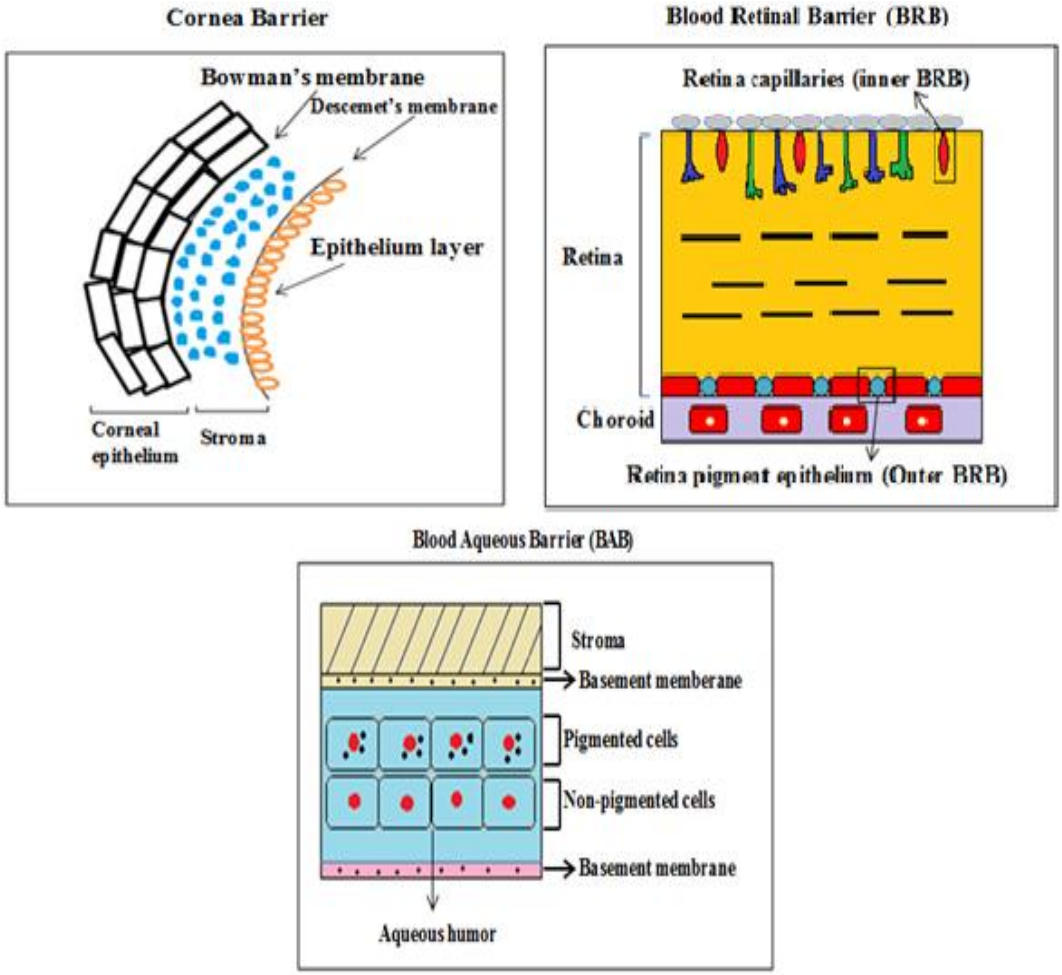

Figure No 2: The critical barriers to ocular drug delivery systems: the Corneal Barrier: involves of epithelial layers attached together by tight junctions avoiding entry of drug particle followed by thick stroma and endothelial cells. The Blood Retinal Barrier (BRB): comprises of the inner BRB resulted from retinal capillaries. Blood Aqueous Barrier (BAB): made by the nonpigmented cells of the epithelium of the ciliary body, and the endothelium of the iris blood vessels.

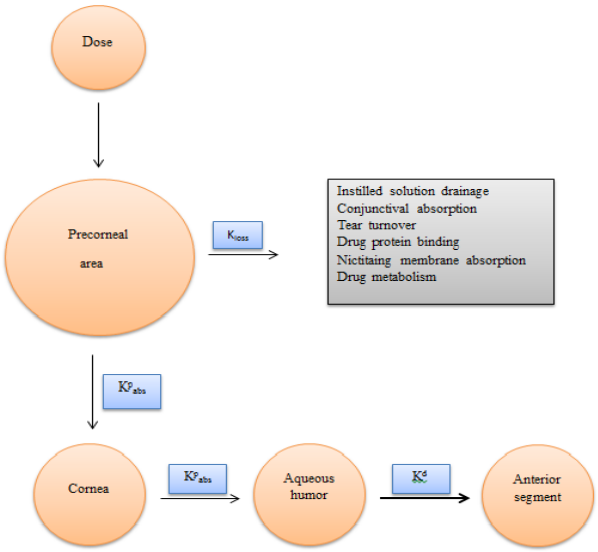

Figure No 3: Model showing precorneal and intraocular events following topical ocular administration of the drug.

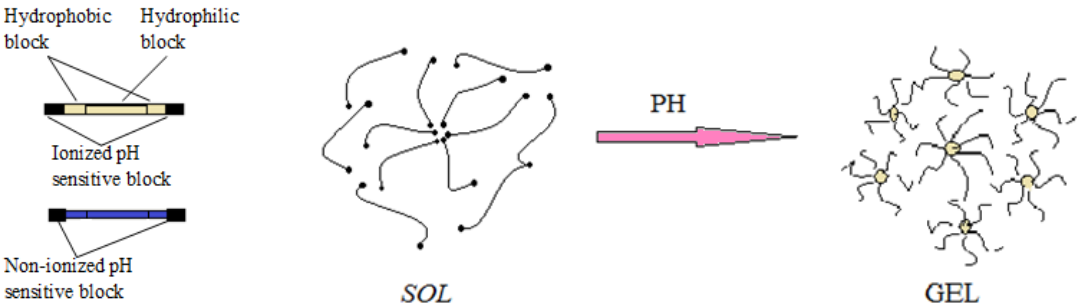

Figure No 4: Mechanism of pH triggered in situ gel system.

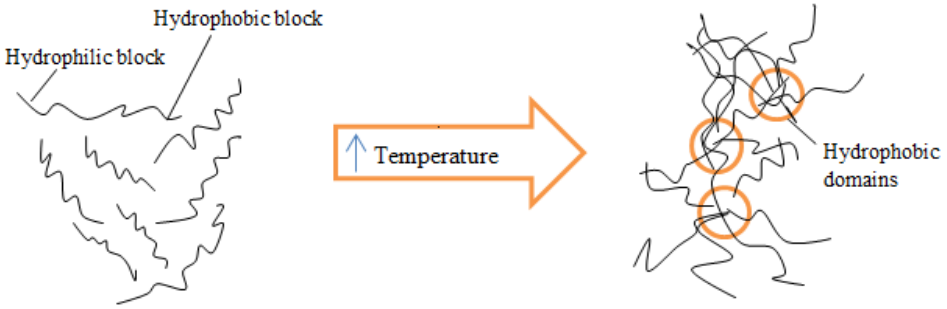

Figure No 5: Mechanism of temperature sensitive system.

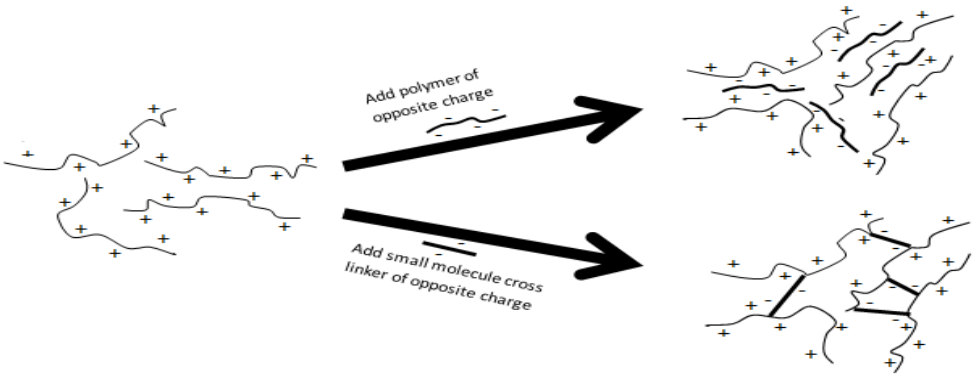

Figure No 6: Mechanism of temperature sensitive system.

Table No1: Different routes and dosage forms for ocular drug delivery.

Sr no.	Route	Dosage form	Benefits	Constraints
1.	Topical	Solutions	Ease of administration	Poor bioavailability, suitable only for anterior segment, blurring vision[5]
		suspensions	Patient compliance. Best for drug with slow dissolution.	Drug properties decide performance. Loss of each solution and suspended solid.[15]
		ointments	Flexibility in drug selection. Improved drug stability. Resistance to nasolacrimal evacuation inhibition of dilution with the aid of tears.	Sticking of eyelids. Blurred vision. Poor patient compliance. Drug choice limited by partition coefficient.[5]
		Emulsions	Prolonged release of drug from vehicle.	Blurred vision. Patient's non-compliance. Possible oil entrapment.[15]
		Gels	Comfortable. Less blurred vision.	Matted eyelids after use. No rate control on diffusion.[10]
2.	subconjuctival	injectable	Delivery of large molecular size drugs, sustained release of drug.	Patient non-compliance, suitable for only water soluble drugs.[5]
3.	Retrobulbar	Injectables (used for anesthetization)	-	Perforation of globe, affected person non-compliance.[5]
4.	Peribulbulbar	Injectables (used for anesthetization)	Avoidance of perforation of globe	Non-compliance in paediatrics sufferers and patient with mental disorders[5]
5.	Intracmeral	Injectables	Sustained delivery to aqueous humor	Patient non-compliance.[5]
6.	Intraviteral	Injectables	Sustained delivery of drug to posterior section of the eye	Patient non-compliance.[13]

Table No 2: Different in situ gelling polymers.

Polymer	Mechanism	Properties
In Temperature Sensitive In Situ Gelling System		
1. POLOXAMER/ PLURONICS	At room temperature (25^0C), it behaves as viscous liquid and is transformed to transparent gel when temperature increases (37^0C). At low temperature, it forms small micellar submit in solution and increase in temperature results increase in viscosity leads to swelling to form large micellar cross linked network.	Poloxamers or pluronic are the series of commercially available difunctional triblock copolymers of non-ionic nature. They incorporate of a central block of relatively hydrophobic polypropylene oxide surrounded on each sides by means of the blocks of relatively hydrophilic poly ethylene oxide. The pluronic triblock copolymers are available in various grades differing in molecular weights and physical forms.[17]
2.CELLULOSE DERIVATIVES (Methyl Cellulose, Hydroxy Propyl Methyl Cellulose, Ethyl Hydroxy Ethyl Cellulose)	Gelation of cellulose solution is caused by hydrophobic interactions between molecules containing methoxy substitution. At low temperature, molecules are hydrated and little polymer-polymer interaction occurs, whereas at high temperature, polymers lose their water of hydration	Cellulose is a linear homopolymer polysaccharide consisting of D-anhydroglucopyranose units joined together by β-1,4-glycosidic bonds. Extensive intramolecular and intermolecular hydrogen bonding present in cellulose renders it insoluble in water. Various cellulose ethers (CEs) have been prepared via etherification of the three hydroxyl groups on anhydroglucose units of cellulose producing water-soluble derivatives.[5]
3.GUAR GUM	As guar gum has the capability of forming high viscous solution at low concentrations. As guar gum is soluble in both hot water and cold water, temperature plays a key	Guar gum is a naturally occurring gum which is also called as guaran which is obtained from the reproductive structure (endosperm) of the seed. Guar gum is soluble in water but insoluble in

	role in the formation of gelling in the solution. So, increase in temperature causes reduction in gelling property of guar gum. As the temperature reduces and causes the formation of sol. So, temperature causes reversible change in gelling of gaur gum.	hydrocarbons, fats, esters, alcohols and ketones. Guar gum has derivatives that are used in targeted delivery systems in the formation of coating matrix systems, nano-microparticles and hydrogels. The semi synthetic form of guar gum is carboxy methyl guar(CMG) which is anionic in nature that are used in formulation of transdermal drug delivery systems because it shows good release rate profile, safety and stability.[20]
In pH Sensitive In Situ Gelling System		
1. CARBOPOL	At specific pH there is Electrostatic, hydrophobic interaction and Hydrogen bonding takes place, hence leads to interdiffusion. The observed phase transition for carbopol solution was mediated by the variation of pH from 4.0 to 7.4 and can be attributed to ionization of Carbopol polymer.	Carbopol is the lightly crosslinked commercial form of Poly(acrylic acid), which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. As the concentration of carbopol increases, due to its acidic nature it causes irritation to the eye. Addition of viscosity enhancer like HPMC, MC will reduce the concentration without affecting its gelling property.[4]
2. POLYCARBOPHILS	Polycarbophil is insoluble in water, but its high swelling capacity in a neutral medium permits the entanglement of the polymer chains with the mucus layer. The nonionized carboxylic acid groups of polycarbophil bind to the mucin by means of hydrogen bonds.	Polycarbophil is also the lightly crosslinked commercial form of Poly (acrylic acid) exhibits stronger mucoadhesion same as Carbopol. As concentration increases, acidic nature may cause lacrimation, hence combination of polymers are used.[5]
In Ion Sensitive In Situ Gelling System		
1. GELLAN GUM/GELRITE	Gellan gum produce a cation induced in situ gelation (Ca2+, Mg 2+, K+, Na+) due to the cross linking between negatively charged helices and mono or divalent cations (Na+, Ca+, Mg+) present in tear fluid.	Gellan gum is anionic heteropolysaccharide that is, tetrasaccharide repeat unit of 2 β-D-glucoses, 1 β-D-glucuronate, and 1 α-L-rhamnose. Gelrite R is a low-acetyl Gellan gum, which forms a clear gel in the presence of mono- or divalent cations. It has the tendency of gelation which is temperature dependent or cations induced.[6]
2. ALGINATES	The monomers of alginate (β-D-mannuronic acid (M) and α-L- glucuronic acid (G) are arranged as M-M block or G-G block with alternating sequence (M-G) block. Upon interaction of G block of polymer with calcium moieties in tear fluid, resulting in the formation of homogenous gel.	It consist of (1→ 4) linked β- D-mannuronic acid and α-L-guluronic acid. A prolonged precorneal residence of formulations containing alginic acid looked for, not only based on its ability to gel in the eye but also because of its mucoadhesive properties.[26]
3. XANTHAN GUM	The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain which results in gel formation when comes in contact with (ions present in) tear fluid.	The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β-D glucoseresidues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronicacid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain.[21]

Table No 3: Example of Different In Situ Gelling Systems.

Drug	Polymer	Mechanism	Reference
Sinomenine Hcl	Carbopol 940 and HPMC K4M	PH	1
Baicalin	Carbopol 974P and HPMC E4M	PH	24
Timolol maleate	Carbopol/Chitosan	PH	3
Ciprofloxacin	Carbopol 940 and Methocel E50LV	PH	1
Pilocarpin Hcl	Carbopol 940	PH	1
Ofloxacin	Carbopol 940 and Methocel E50LV	PH	3
Ketorolac	Carbopol 940 and HPMC-K15M,HPMC-44M	PH	1
Dexamethasone sodium phosphate	Carbopol 940	PH	27
Sparfloxacin	HPMC and Carbopol	PH	28
Betoxolol	Pluronic F-127 and HPMC-E50LV	Temperature	3
Timolol maleate	Poly(N-isopropyl acrylamide)	Temperature	3
Lomefloxacin Hcl	Pluronic 127, pluronic 68 and Alginate	Temperature	29
Fluconazole	Poloxamer 407 and HPMC	Temperature	30
Moxifloxacin Hcl	Poloxamer 407 and Poloxamer 188	Temperature	31
Brimonidine Tartarate	Carbopol 974 and HPMC E4M	Ion	32
Acetazolamide	Gellan/Xanthan, Gellan/HPMC	Ion	32
Chloramphenicol	Gellan gum	Ion	27
Fluconazole	Alginate and HPMC	Ion	30
Gatifloxacin	HPMC	Ion	31

CONCLUSION

The development of in situ gel systems for ophthalmic drug delivery provides simplest and best gel-forming systems and has been proved advantageous over other conventional dosage forms. These advantages include sustained and prolonged release of drug (like hydrogel), good stability, biocompatibility, ease of installation (like solution), etc. It is an ideal system that maintains effective level of drug for the longer duration following a single application and offers the primary requirement of a successful controlled release product. Use of biodegradable and water soluble polymers for the in situ gel formulations can make them more desirable and excellent drug delivery systems with minimum possibilities of irritation, and hence improved patient compliance.

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