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IN-SITU GELLING OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Eye, which is the most vital organ of the body suffer from various eye problems like glaucoma. Endopthalmitis , dry eye syndrome, trachoma, keratitis, conjunctivitis etc. Most ocular diseases are treated by topical drug application in the form of solutions, suspensions and ointment. These conventional dosage forms suffer from the problems of poor ocular bioavailability because of dilution and rapid drainage. Prolonged drug delivery can be achieved by various new dosage forms like in-situ gel, collagen shield , minidisc, ocular film, ocusert , nanosuspension, nanoparticulate system, liposomes, niosomes, dendrimers, ocular iontophoresis etc. The most successful of these is the in-situ forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible liquid-gel phase transition. The aim of this article is to present a concise review of in-situ gelling system to overcome all above problems. This review also summarizes various 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.

Keywords: in situ gel, novel drug delivery system, polymers.

Introduction:

The eye is a complex and unique part of the human organs that has been considered as the window to the human soul. Broadly, the human eye is divided into two segments that are anterior and posterior segments . The specific dis- ease conditions of the eye are associated with each of these broad segments. For instance, conjunctivitis, glaucoma, ble- pharitis, and cataract are some of the diseases that affect the anterior segment of the eye, while diabetic retinopathy and age-related macular degeneration are known to affect the pos- terior segment [1] Due to the unique structure of the eye, which inhibits the entry of drug molecules into the desired site, the ophthalmic delivery of the drug has been one of the most challenging tasks for a pharmaceutical scientist. Eye drops accounts for more than 90% of ophthalmic preparations on the markets. However, they are washed away from the eye and results. in low ocular bioavailability Due to the unique structure of the eye, which inhibits the entry of drug molecules into the desired site, the ophthalmic delivery of the drug has been one of the most challenging tasks for a pharmaceutical scientist. Eye drops accounts for more than 90% of ophthalmic preparations on the markets. However, they are washed away from the eye and results. in low ocular bioavailability after topical administration by different elimination mechanisms[2]. This elimination process includes tear turnover, nasolacrimal drainage, protein binding, systemic absorption, enzymatic degradation and complex penetration barriers Corneal Barrier, Blood Aqueous Barrier (BAB).

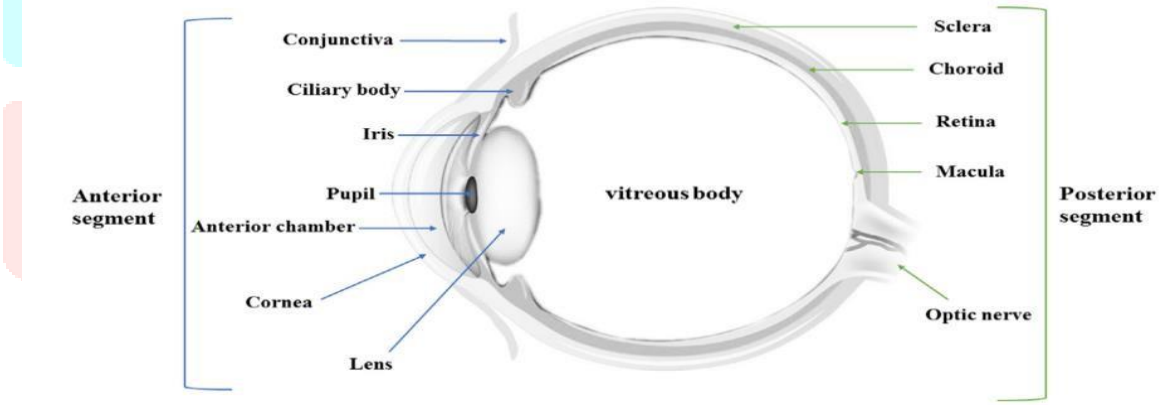

Fig 1 The anatomy of ocular system: the anterior segment involves conjunctiva, ciliary body, iris, pupil, anterior chamber, cornea and lens; the posterior segment consists of sclera, choroid, retina, macula and optic nerve.[3]

One of the main drawbacks in ocular drug delivery is achieving and retaining of optimal concentration of drug at the desired site of action in the eye. Several ophthalmic dosage forms such as ointments, eye drop solutions, gels, and ocular inserts have been investigated in order to prolong the ocular residence time of drugs after the topical application to the eye. With these formulations, the corneal contact time has been increased to some extent. But, due to blurred vision and poor patient compliance resulted from ointments and inserts, re- spectively, they have not been fully accepted . Furthermore, drugs that are administered systemically to exert their action in the ophthalmic system also have known to access poorly to the eye tissue . Intravitreal and pertiocular routes are recommended in order to deliver drugs to posterior part of the eye.However, there are disadvantages associated with these routes like the frequent intravitreal injections could be painful, thus affecting a patient compliance. The periocular route is easy for administration, but the static and dynamic barriers constitute a problem. The low bioavailability of medications from the conven- tional delivery system is resulted from a great extent of precorneal drug loss by nasolachrymal drainage. The rapid clearance of the

topically applied drug into the eye often results in a short duration of pharmacological activity and, therefore, the need for a frequent dosing regimen. Moreover, 50%-100% of an instilled dose could undergo systemic absorption through drainage via the nasolachrymal duct. This could lead to a possible increased risk of unwanted systemic toxic effects .[4]

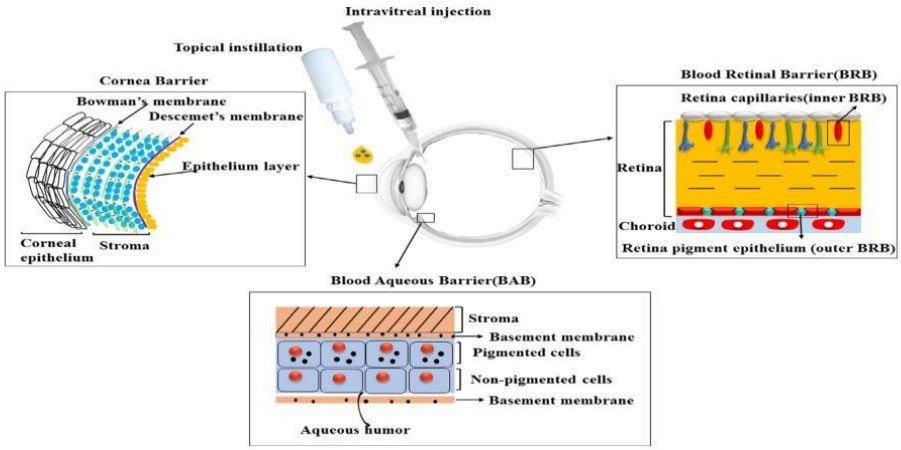

Fig. 2 - The critical barriers to ocular drug delivery systems; the Corneal Barrier: involves of epithelial layers attached together by tight junctions avoiding entry of drug particle followed by thick stroma and endothelial cells. The Blood Retinal Barrier (BRB): comprises of the inner BRB resulted 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.(5)

In-situ gelling system is one of the promising approaches to improve the retention time of drugs on the ocular surface. After instillation of the aqueous solution containing stimuliresponsive poly- mers such as pH-sensitive polymers, thermosensitive poly- mers, and ionsensitive polymers, the viscous and mucoad- hesive gels are formed on the eye surface, subsequently, ocular retention time and ocular bioavailability of the oph- thalmic drugs are improved. Therefore, in this review, we sum- marized and discussed the most recent research innovations. [6][7]

Advantages:

• Controlled and sustained release of the drug.

• Ease of the drug administration.

• It can be administered to unconscious patients.

• More patient compliance and comfort.

• Minimizing the dose frequency and drug toxicity.

• Increased bioavailability.

• Use of natural polymers provide biocompatibility and biodegradation.

• Natural polymers have inherent properties of biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities.

• In situ gels offer an important "stealth" characteristic in vivo, owing to their hydrophilicity which increases the in vivo circulation time of the delivery device by evading the host immune response and decreasing phagocytic activities.[8]

Disadvantages:

• It requires high level of fluids.

• The sol form of the drug is more susceptible for degradation.

• After placing the drug eating and drinking may become restricted up to few hours.

• Lower mechanical strength, may result into premature dissolution or flow away of the hydrogel from a targeted local site.[9]

Anatomy of the ocular system:

Generally, the eye is divided into two important segments: The anterior segment which involves the cornea, conjunctiva, iris, pupil, ciliary body, anterior chamber, aqueous humor, lens and trabecular meshwork. The posterior segment includes vitreous humor, sclera, retina, choroid,macula and optic nerve.(Fig. 1)

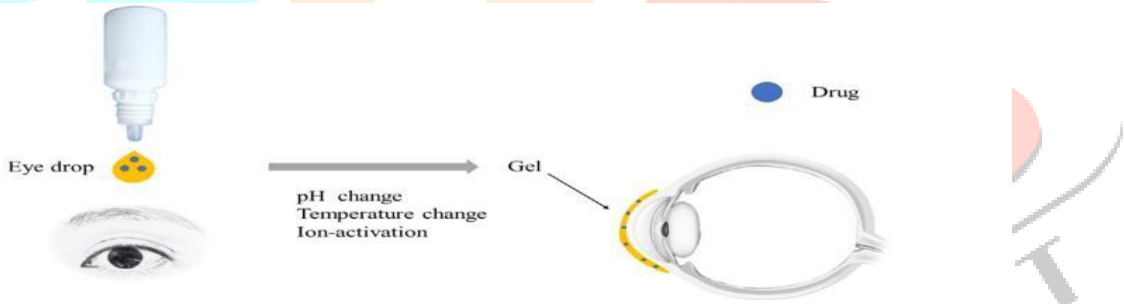

Fig 3 -In-situ forming gels process. The formulation is liquid when instilled into the eye which undergoes gel formation rapidly in the cul-de-sac of the eye in response to environmental changes such as pH, temperature and ion; finally release the drug slowly under physiological conditions.(10)

Corneal permeability is the most essential factor that determines drug concentration in aqueous humor. For most of hydrophilic drugs, the epithelium is a rate-limiting barrier of transcorneal diffusion of drugs . The stroma is owing to the hydrophilic nature, it acts as a barrier for the diffusion of highly lipophilic drugs . The corneal stroma is mainly consisting of charged and highly organized hydrophilic collagen that inhibit the diffusion of hydrophobic molecules . Conjunctiva is a clear thin membrane that covers the sclera and lines the inner surface of the eyelid. It is consist of stratified epithelium (non-keratinized) and goblet cells. It provides protection to the eyes by secreting mucus that prevents entry of microorganisms and lubricating the eyes . In humans, the conjunctiva occupies a 17-times larger surface area than the cornea. This allows for greater absorption of the drug to occur through the conjunctiva. However, absorption of the drug via the conjunctiva is still not significant due to the existence of conjunctival blood capillaries and lymphatics, which leads to a considerable loss of drug

into the systemic circulation, thereby reducing the overall ocular bioavailability . Aqueous humor consists of clear liquid that fills both the posterior and anterior chambers of the eye.[11]

The aqueous humor is non-vascular structure that must be transparent to allow light transmission, which provides nutrition for the cornea . It contains excessive concentration of ascorbate which is about 15-fold the concentration in the plasma, and has a pH of 7.2 . Its main function is to provide nutrients, eliminate waste from non-vascular tissues and control the intraocular pressure that keeps the convex shape of the cornea . The retina is a multiple layers and complex structure that consists of vascular, glial and neural, cells and nerve fibers . The retina is a major barrier to ocular delivery of drug with larger molecular weight .[12]

In-situ gelling system:

Ophthalmic in-situ gelling is comprising of environmentally sensitive polymers that will be altered structurally with the small changes in specific conditions like pH, temperature and ionic strength in the environment. In-situ forming gels are liquids during instillation into the eye and then undergoes rapid gelation in the cul-de-sac of the eye to form viscoelastic gels in response to environmental changes (Fig. 3); lastly release the drug slowly under physiological conditions .Consequently, the residence time of the gel formed in-situ will be extended and the drug is released in a sustained manner which leads to enhanced bioavailability, minimized systemic absorption and reduced frequent dosing regimen resulting to improved patient compliance.

Mechanisms of gelling system In-situ gel formation may be achieved by a number of mechanisms including temperature- (Fig. 4), pH- and ion-activated systems. Temperature triggered in-situ gel system which utilizes the temperature sensitive polymers that exist as a liquid form below its low critical solution temperature (LCST) and undergoes gelation when the environmental temperature reaches or is above the LCST . The pH induced in-situ gel contains polymers which possess acidic or alkaline functional groups within the chain molecule and undergoes a sol-gel phase transition on change from a low pH to high pH environment . Ion-activated systems are also known as osmotically triggered in-situ gel systems wherein the polymer undergoes a sol-gel transition due to changes of ionic concentration, which is typically triggered by mono or divalent cations in tear fluid particularly Na+, Mg2+and Ca2+. In addition, sol-gel phase transition has known to be induced by enzymatic cross linking and photon polymerization . and the concern of this review. [13]

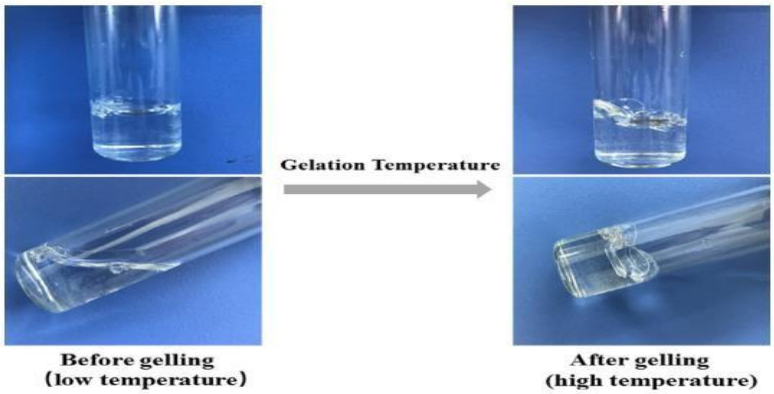

Fig. 4-The gelation process of thermosensitive in-situ gelling. When the temperature is below the gelation temperature (GT), it is clear solution with low viscosity, upon heating it to GT, the solution is converted to the gel with high viscosity.[14]

Stimuli-responsive in-situ gel system. Temperature-triggered in-situ gel systems The temperature sensitive in-situ gel is the oldest, the most extensively studied and common type of stimuli-responsive gel. It can be easily and precisely introduced into the eye in liquid form without producing irritation or blurred vision. The gel is formed at the precorneal temperature (35 °C) to endure the lachrymal fluid dilution without rapid precorneal elimination of instilled drug after administration . It has been recommended that a good thermo-responsive ocular insitu gel should possess the gelation temperature above the room temperature and undergo gelsol transition at a pre-cornealtemperature in order to avoid storing in a refrigerator before instillation, which may sometimes result in eye irritation due to cold nature . Polymers used in temperature triggered in-situ gel systems Poloxamers (Pluronic) Poloxamers are a triblock copolymer poly (ethylene oxide)- b-poly (propylene oxide)-b-poly (ethylene oxide) (PEOPPOPEO) exhibiting amphiphilic nature because of hydrophilic ethylene oxide domains and hydrophobic propylene oxide domains The triple block of copolymers PEO-PPOPEO (Pluronics or Poloxamers) undergo gelation at body temperature in concentrations above 15% (w/w) . The principal possible mechanisms have been proposed to explain the sol-gel phase transition at an increased temperature are the gradual desolvation of the polymer, enhanced micellar aggregation, and the increased entanglement of the polymeric network . The pluronic triblock copolymers are existing on the market in different grades with different physical forms and molecular weights. Depending upon the physical description for the grades are given as L for liquid, P for paste and F for flakes.[16]

Xyloglucan:

Xyloglucan is a polysaccharide obtained from tamarind seeds, therefore it is often named tamarind seed polysaccharide (TSP), which when partially degraded by β-galactosidase displays thermally reversible gel formation in diluted aqueous solution . The sol-gel transition temperature is varying with the degree of galactose degradation. TSP gels have been reported to have a potential for oral, ocular, intraperitonial and rectal drug delive . TSP is highly watersoluble and gelation occurs when the galactose elimination exceeds 35%.[17]

Table 1 – Some examples of thermo-sensitive in-situ gelling system.

Model drugs	Polymers	Major finding	Ref.
Brinzolamide	Poloxamer F127 and carbopol 934P	A sol-gel at 33.2 ± 1.1 °C controlled release of drug over a period of 8 h.	[41]
Ofloxacin	Pluronic (PF-127 and PF-68) and sodium alginate	*In vivo* evalutaion in rabbits exhibited inproved retention performance of 20% (w/w) Pluronic F127 compared to Pluronic F68.	[42]
Ketorolac tromethamine	Pluronic F-127 HPMC K4M	Improved its ocular availability and prolonged its residence time.	[45]
Sparfloxacin	Pluronic (PF 127 and PF 68)	Showed promising antimicrobial activity in vitro and in vivo.	[51]
Fluconazole	Poloxamer/tween/carbopol	The in vivo ophthalmic absorption was superior to the conventional eye drop.	[52]
Lomefloxacin	Pluronic F127, Pluronic F68 and sodium alginate	Revealed a sustained release profile of 8 h.	[53]
Methazolamide	Poloxamer 407 and poloxamer P188	Had a better ability to retain drug than the eyedrops.	[54]
Diclofenac sodium	Pluronic F127	The bioavailability of diclofenac sodium in aqueous humor was significantly increased.	[55]
Dorzolamide hydrochloride	Poloxamer 407 and Poloxamer 188	Better pharmacological effect, faster onset of action, and prolonged effect relative to either drug solution or the market product.	[56]

Cellulose:

Derivatives Cellulose is a polysaccharide containing a linear chain made up of several hundred to over ten thousand β (1→4) linked d-glucose units. The cellulose derivatives used in topical ophthalmic formulations are methyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (NaCMC) . At low concentrations (1–10%), their aqueous solutions exist as a liquid but form gels upon heating. The high phase transition temperature exhibited by cellulose derivatives can be lowered by physical or chemical modification . The transition temperature is between 40 and 50 °C for MC and between 75 and 90 °C for HPMC. Addition of sodium chloride is known to lowers the gelation temperature of MC to 32–34 °C, while the transition temperature of HPMC can be decreased to about 40 °C by lowering the hydroxypropyl molar substitution. [18] Chitosan:

Chitosan is an aminopolysaccharide made from the partial deacetylation and depolymerization of chitin, which is found in the exoskeletons of arthropods, such as crustaceans Commercially, chitin is mainly derived from the shell wastes of shrimp, crab, krill, lobster, and squid .Chitosan has been proven to possess many advantages in biomedical applications due to its biocompatibility, biodegradability, mucoadhesiveness with low immunogenicity and low cytotoxicity . Recently, chitosan-based thermosensitive gels with different polyols such as ethylene glycol, glycerol, and sorbitol have attained much popularity. The derivatization of primary amino groups of chitosan (CS) by thiol groups results in the formation of Thiolated Chitosan (TCS). TCS based drug delivery system is gaining attention because it exhibits high mucoadhesive strength and extended drug release properties. TCS shows in-situ gelling properties because of the formation of intra and intermolecular disulfide bonds as a result of oxidation of thiol groups at physiological pH-values. Research progress in temperature triggered in-situ gel systems Over the last decades, a large number of studies on temperature triggered in-situ forming system have been reported .To mention some of them, Li et al.formulated Brinzolamide drug-resin in-situ thermosensitive gelling system, using Poloxamer F127 in combination with Carbopol 934P. The optimal formulation displayed a gel formation at 33.2 ± 1.1 °C and the diffusion-controlled release of the model drug over a period of 8 h. The in vivo study suggested that the in-situ gel demonstrated a better ability in retaining the drug than commercial formulations. [19]

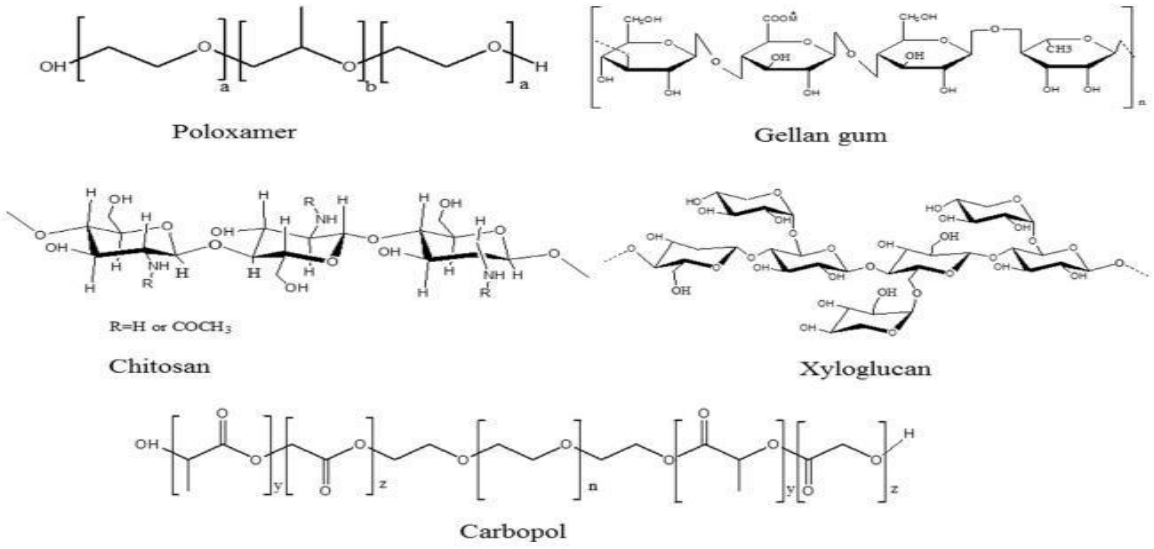

Fig. 5 – The chemical structure of some in-situ gel polymers.

Al-Khateb et al. also investigated the in-situ gelling system containing ofloxacin using a combination of Pluronic (PF127 and PF-68) and sodium alginate. The incorporation of Pluronic F68 to Pluronic F127 solutions was found to rises the sol-gel temperature of binary formulation to above the physiological range of temperatures. The superior in vitro drug retention performance on glass surfaces and freshly excised bovine corn were exhibited by 20% (w/w) Pluronic F127 in comparison with other formulations. Additionally, in vivo evaluation in rabbits demonstrated that a retention performance of 20% (w/w) Pluronic F127 was higher than that of Pluronic F68. Furthermore, the slug mucosa irritation assay and bovine corneal erosion studies demonstrated no significant irritation was observed that resulted from these polymers and their combinations. [20]

Osswald et al. prepared an injectable microspherehydrogel by loading the antivascular endothelial growth factor, anti-VEGF (ranibizumab or aflibercept) into poly (lactic-co-glycolic acid) microspheres that were then suspended within an injectable poly(N-isopropylacrylamide)- based thermo-responsive hydrogel DDS. The efficacy was evaluated in vivo in a laser-induced rat model of choroidal neovascularization (CNV). CNV lesion area was measured and quantified by fluorescein angiograms and a multi-Otsu thresholding technique, respectively. Intraocular pressure (IOP) and dark-adapted electroretinogram (ERG) were also measured pre- and post-treatment (1, 2, 4, 8, and 12 weeks). The result has shown that the antiVEGF-loaded DDS group had exhibited significantly smaller CNV lesion areas than a nontreatment group of animals throughout the study, which suggests that the DDS offer a significant benefit in the management of posterior segment eye diseases The addition of cellulose derivates to Pluronic F12 hydrogels assist in increasing the bioavailability of the insitu gel , Morsi et al., prepared Ketorolac tromethamine Nano dispersions formulated into thermo-sensitive in-situ gel using Eudragit RL100. The study demonstrated that reducing the concentration of Pluronic F-127 was found to increase the gelation time and gelling temperature of the in-situ gels. The incorporation of HPMC to pluronic F12 hydrogels has significantly improved the mucoadhesive strength of the gel . Addition of salts (NaCl and KCl) to in-situ gel system has known to decrease the gelation temperature. Bhowmik et al. examined the influence of different salts on the gelation properties, rheology and drug release of in-situ gel based on methylcellulose (MC). The mixture of poloxamer with a mucoadhesive agent (chitosan) is known to extend the retention time of drugs for the treatment of ophthalmic diseases. Gratieri et al. formulated in-situ forming gel consisting the combination of poloxameer and chitosan. The results demonstrated that the addition of chitosan could improve the mechanical strength as well as texture properties of poloxamer formulations and the in-situ gel increased a four-fold retention time in comparison with a conventional solution. In addition to Poloxamer, Poly (N-isopropylacrylamide) (PN) has been widely used as thermo-responsive polymers. For instance, Hsiue et al. developed ophthalmic formulation using PN as the thermosensitive polymer. The clear solution of PN was known to form a gel upon the raising of temperature from the room temperature to about 32 °C. Epinephrine-loaded linear PN and crosslinked PN nanoparticles were developed and evaluated. The finding of the study showed that the pressure decreasing the activity of the formulation with linear PN and combination of linear PN and crosslinked nanoparticles lasted six-fold and eight-fold longer than that of the conventional eye drop, respectively . Recently, the studies have shown that copolymerization of PN with hyaluronic acid (HA) has increased the LCST of PN from 32 °C to above body temperature, which is more appropriate for the ophthalmic application. With this aim, Zhu et al. developed thermo-sensitive in-situ forming gelling formulation of Ketoconazole (KCL) based on PN/HA. The in vitro gelation, drug release, and antifungal activity were evaluated for the developed formulations. The gelation temperature of the PN–HA thermo-gelling solution was found 33 °C. The moderate release of KCL from in-situ gels without burst effects was exhibited. No macroscopic signs of irritation, redness, or other toxic effects were observed. The in vivo antimicrobial study indicated that KCL PN–HA in-situ gels displayed an improved cure percent as compared with commercial eye drops . Very recently, Iohara et al. developed a hydrophobically modified hydroxypropyl

methylcellulose (HM-HPMC) gel formed thermoresponsive hydrogels by incorporation of small amount of α-Cyclodextrin (α-CD) into the solution. .2.2. pH triggered in-situ gelling systems This in-situ gelling system consists of pHsensitive polymers which are polyelectrolytes contain an acidic (carboxylic or sulfonic) or a basic group (ammonium salts) that either accept or release protons in response to alteration in pH in the surrounding environment. At lower pH (pH 4.4), the formulation exists as a regular solution, however, it undergoes gel formation at pH 7.4, that is the pH of tear fluid. [21] Polymers used in pH triggered in-situ gel systems:

Carbopol is a polyacrylic acid (PAA) polymer , that displays a sol-gel phase transition in aqueous solution as a result of raising the pH above its pK of about 5.5 . The carboxylic groups of PAA accept and release protons at low Ph. values and high pH values, respectively. Therefore, at high pH, the PAA swells due to the electrostatic repulsion of the negatively charged groups, releasing the drug molecules to the environment . It is extensively exploited in ocular formulation with the aim of improving pre-corneal retention time of drugs. Carbopol provides the benefit of exhibiting superior mucoadhesive properties as compared to other polymers. Mucoadhesive properties of carbopol is attributed to the interaction of poly(acrylic acid) with mucin that occurs by four mechanisms viz. electrostatic interaction, hydrogen bonding, hydrophobic interaction and inter diffusion . Despite carbopol displays excellent mucoadhesive properties, the acidic nature of the gel is a major drawback which leads to irritation and damage to the eye tissues.Therefore, combinations of carbopol with other polymers including chitosan and HPMC were subsequently developed to overwhelmed this problem.

Ion-activated in-situ gel system:

Ion-activated in-situ gelling systems form a crosslink with cations exists in the tear fluid (Na+, Ca2+ and Mg2+), thus forming a gel on the ocular surface, which give rise to an extended corneal contact time.

Polymers used in Ion-activated in-situ gel system:

The most commonly used ion-activated polymers in ocular formulations are gellan gum (Gelrite®), hyaluronic acid and sodium alginates.

Gellan gum:

Gellan gum are polysaccharides that can be used to induce ion-sensitive hydrogels. It is a linear anionic heteropolysaccharide made up of a tetrasaccharide repeating unit of glucose, glucuronic acid and rhamnose in the ratio of 2:1:1. Gellan comprises hydroxyl and carboxylic functional groups, which may interact with other polymers via hydrogen bonding and/or electrostatic attractions . A low-acetyl gellan gum is commonly available in the market as Gelrite®, which undergoes gelation in the presence of mono- or divalent cations. The electrolytes of the tear fluid especially Na+, Mg2+ and Ca2+ cations are particularly known to induce gel formation of the polymer upon instillation as a liquid solution into the cul-de-sac . The incorporation of optimal quantities of calcium gluconate to gellan formulations lead to the formation of gellan calcium gluconate-simulated tear fluid (STF) gels with a significantly higher strength than when gellan alone was

mixed with STF It undergoes gelation by both temperature sensitive or cations induced mechanism. The possible mechanism of gelation includes the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by hydrogen bonding with water and complexation with cations [22].

Alginate/ Alginic acid:

Alginate is a linear co-polysaccharide derived from brown seaweeds and some bacteria. Chemically it is a (1–4)-linked block copolymer of â-d-mannuronate (M) and its C-5 epimerAlginate/ Alginic acid Alginate is a linear co-polysaccharide derived from brown seaweeds and some bacteria. Chemically it is a (1–4)-linked block copolymer of â-dmannuronate (M) and its C-5 epimer.

Pectin Pectins are a polysaccharides family, where the polymer backbone mostly consists of α(1,4)-d-galacturonic acid residues. Low methoxy pectins which are with a degree of esterification Research progress in ion-activated in-situ gel systems Various ion-activated insitu gelling systems have previously been reported. Rupenthal et al .formulated ion-activated in-situ based on gellan gum, xanthan gum and carrageenan, and in vivo release, precorneal retention time and the ocular irritancy were characterized for the formulations. The results showed that the in-situ system was non-irritant with increased AUC and the miotic response of pilocarpine by 2.5-fold compared to an aqueous solution The in-situ gels exhibited a characteristic sustained and extended drug effects behavior compared with the conventional eye drops at the same dose . Kesarla et al. formulated nanoparticles-loaded ophthalmic in-situ gel using the ion-sensitive polymer gellan gum used as a gelling agent which could form gel immediately and remained for the extended time of period. The developed formulation was found stable and displayed improved corneal contact time and minimizing the frequency of administration. . Tayel et al. developed a novel ion-sensitive in-situ ophthalmic nanoemulsion (NE) gels containing terbinafine hydrochloride. The optimized in-situ NE gel exhibited a significantly higher Cmax, delayed tmax, prolonged mean residence time and enhanced ocular bioavailability. [23]

Multi-stimuli responsive in-situ gel:

One of the recent excellent strategies in ocular in-situ gelling system is the use of a combination of polymers with the different gelling mechanism, which have shown an improved therapeutic efficacy and better patient compliance Over last current years, a number of investigations that involved the combination of thermo-responsive polymers, pH-sensitive polymers or ion-activated polymers in the same ophthalmic formulation have been reported . Khan et al. developed and evaluated sparfloxacin-loaded novel in-situ gelling system for sustained ophthalmic drug delivery using a combination of ion and pH activated gelling system, which were sodium alginate and methylcellulose, respectively. The formulation was in sol form at pH (4.7) and has undergone quick sol-gel transition upon raising pH to 7.4. The insitu gel formulation demonstrated in vitro sustained release of sparfloxacin over a period of 24 h as compared to eye drop. [24].

Polymers used as in situ gelling agents:

- Pectin:

Pectins are a family of polysaccharides, in which the polymer contains mainly, comprises α- -(1-4)--D galacturonic acid residues. In the presence of free calcium ions, Low methoxy pectins (degree of esterificationreadily forms gels in rosslink the galacturonic acid chains in a manner described by egg-box model. In the presence of H+ ions the gelation of pectin will occur, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery. Pectin used mainly for these formulations is that it is water soluble, so organic solvents are not used in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is orallyadministered.[25]

- Guar gum ~Properties:

Guar gum is also called as guaran of naturally occurring gum which is obtained from the endosperm of the seed. Guar gum is insoluble in hydrocarbons, fats, esters, alcohols and ketones but soluble in water. These show its dispersibility in both cold and hot water that it is soluble in both cold and hot water to form colloidal solution at low amount. Guar gum has derivatives are used in targeted delivery systems in the formation of coating matrix systems, nano-microparticles and hydrogels. Guar gum also has derivatives such as graft polymers like polyacrylamide grafted guar gums that have good colon targeting properties. It can also be used as a polymer in matrix tablets which shows controlle.

- Gellan gum ~Properties:

Gellan gum is an anionic hetero polysaccharide, secreted by microbe Sphingomonas elodea. It consists of glucose, rhamnose, glucuronic acid and linked together to obtained a tetrasaccharide unit. Gelriteis deacetylated gellan gum, obtained by treating gellan gum with alkali to remove the acetyl group in the molecule. Due to instillation, gelrite forms gel because in presence of calcium ions. The gelation includes the formation of double helical junction zones followed by aggregation of double helical segment to form three dimensional networks by complexaton with cations and hydrogen bonding with water. In food industry, gellan gum is used as suspending and stabilizing agent.[26]

- Chitosan ~Properties:

Gelling of chitosan occurs by two changes such as pH responsive change and temperature change. Chitosan is a natural component of shrimp and crab shell which consist of biodegradable, thermosensitive, polycationic polymer obtained by alkaline deacetylation of chitin. Chitosan is a biocompatible pH dependent cationic polymer, which can remains dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to precipitation by the formation of a hydrated gel.[27]

EVALUATIONS OF THE IN SITU GEL SYSTEM:

Evaluation parameters for in situ gel formulations included clarity, pH measurements, gelling ability, potency, theology studies, in vitro diffusion studies, isotonicity, antimicrobial activity, in vivo rabbit eye test, and accelerated stability studies. will be The formulation should have an optimal viscosity that allows it to be easily instilled into the eye as a liquid (droplet) that undergoes a rapid sol-gel transition (driven by pH, temperature, or ion exchange).

- Physical parameters:

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

- Gelling capacity:

The gelling capacity of the prepared formulation is determined by placing a drop of the formulation in a vial containing 2.0 ml of freshly prepared simulated tear fluid and visually observe.

- Rheological studies

The viscosity measurements can be calculated using Brookfield viscometer, Cone and Plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity of 5-1000 m Pas, before gelling & after formation of gel should have viscosity from about 5050,000 m Pas.

- In vitro drug release studies

In vitro release study of insitu gel solution is carried out by using Franz diffusion cell. The best fit model is check for Krosmeyers Peppas and Fickinian diffusion mechanism for their kinetics

- Texture analysis

The consistency, firmness and cohesiveness of insitu gel are assessed by 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.

- Isotonicity evaluation

Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. All ophthalmic preparations are subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the requisite viscosity.[28]

Clinical application of in-situ gelling:

To date, some of in-situ gel formulations have been commercially available for ocular drug delivery . For instance, Timoptic-XE®, containing timolol maleate (0.25% and 0.5%) in gellan gum has been available on market since 1994, which is applied topically on the eye to treat glaucoma. Furthermore, some of the patents on in-situ gel for ocular delivery system have been issued in the last decades, and are being summarized.[29]

Conclusions:

Despite the challenges in ocular drug delivery, over the past few years,many innovative approaches are being developed to overcome the problems associated with conventional of ophthalmic preparations. The in-situ gelling system is one the promising and extensively studied strategies that could prolong precorneal resident time and offer the sustained release drug delivery, thus improve ocular bioavailability and therapeutic efficacy and reduce systemic absorption and toxicity. Furthermore, due to its drug release sustaining ability and decrease the frequency of administration, in-situ gel could improve patient compliance. In in-situ gel formulation with different stimuli-responsive polymers that have high sensitivity to change in pH, temperature, and ion concentration are used. However, the combination of two or more stimuli-responsive polymers in the same formulation is known to exhibit greater compliance and improved therapeutic efficacy. Moreover, exploring the combination of different drug delivery approaches (i.e. nanoparticles loaded in-situ gelling) to develop in-situ gel has been the attractive strategies to improve ocular drug delivery system. As the eye is the most essential and sensitive part of the body,the safety issues of ophthalmic formulations is critically important. The majorities of the cytotoxicity and irritability studies included in this review showed that no significant alterations or sign oftoxicity due to the application of in-situ gel. However, further studies are required to evaluate the possible toxicity due to repeated and long term applications and materials for the preparation of nanoparticles in nano-gel systems. In addition, the increased viscosity of in-situ gel may cause some limitations like blurred vision and discomfort to patient resulting in a faster elimination due to reflex tears and blinks. Therefore, critical control of the viscosity should be taken into consideration during designing and optimization of in-situ gel formulation in order to reduce the limitations to the tolerable level. At present, most of the ophthalmic in-situ gels were designed only for the formulations containing of single active ingredient. In the future, some more suitable strategies should be developed for the formula consisting of multiple ingredients such as Traditional Chinese Medicine in particular, which involves a multi-target approach to produce their action. Lastly, in the future, we expect the innovation of new and more reliable in-situ forming polymers which may be responsive to some biochemical markers associated with the disease conditions of the eye.

REFERENCES:

[1] Addo E, Bamiro OA, Siwale R. Anatomy of the eye andcommon diseases affecting the eye. In: Addo RT, editor. Ocular drug delivery: Advances, challenges and applications; 2016. p. 11-25.

[2] Joseph RR, Venkatraman SS. Drug delivery to the eye: what benefits do nanocarriers offer. Nanomedicine (Lond) 2017;12(6):683-702.

[3] Zhu M, Wang J, Li N. A novel thermo-sensitive hydrogel-based on poly(Nisopropylacrylamide)/ hyaluronic acid of ketoconazole for ophthalmic delivery. Artif Cells Nanomed Biotechnol 2017. doi:10.1080/21691401.2017.1368024.

[4] Bisht R, Mandal A, Jaiswal JK, Rupenthal ID. Nanocarrier mediated retinal drug delivery: overcoming ocular barriers to treat posterior eye diseases. WIRES Nanomed Nanobiotechnol 2018. doi:10.1002/wnan.1473.

[5] Makwana SB, Patel VA, Parmar SJ. Development and characterization of in-situ gel for ophthalmic formulation containing ciprofloxacin hydrochloride. Results Pharma Sci 2016;6:1-6.

[6] Kaur IP, Smitha R. Penetration enhancers and ocular bioadhesives: two new avenues for ophthalmic drug delivery. Drug Dev Ind Pharm 2002;28(4):353-69. [7] Bamiro OA, Ubale RV, Addo RT. Background of Ocular Drug Delivery. In: Addo RT, editor. Ocular drug delivery: Advances, challenges and applications. Springer International Publishing: 2016. p. 1-9.

[8] Kotreka UK, Davis VL, Adeyeye MC. Development of topical ophthalmic in situ gelforming estradiol delivery system intended for the prevention of age-related cataracts. PLoS One 2017;12(2):e0172306.

[9] Ye T, Yuan K, Zhang W, et al. Prodrugs incorporated into nanotechnology-based drug delivery systems for possible improvement in bioavailability of ocular drugs delivery. Asian J Pharmaceut Sci 2013;8(4):207-17.

[10] Liu Y, Liu J, Zhang X, Zhang R, Huang Y, Wu C. In situ gelling gelrite/alginate formulations as vehicles for ophthalmic drug delivery. AAPS PharmSciTech 2010;11(2):610-20.

[11] Tan G, Yu S, Pan H, et al. Bioadhesive chitosan-loaded liposomes: a more efficient and higher permeable ocular delivery platform for timolol maleate. Int J Biol Macromol 2017;94(Pt A):355-63.

[12] Addo RT, Yeboah KG, Siwale RC, et al. Formulation and characterization of atropine sulfate in albumin-chitosan microparticles for in vivo ocular drug delivery. J Pharm Sci 2015;104(5):1677-90. [13] Biswas GR, Majee SB. Niosomes in ocular drug delivery. Eur Pharmaceut Med Res 2017;4(7):813-19.

[14] Prausnitz MR, Jiang J, Pate SR, et al. In: Ocular drug delivery using microneedles; 2007. p. 3191.

[15] Duan Y, Cai X, Du H, Zhai G. Novel in situ gel systems based on P123/TPCS mixed micelles and gellan gum for ophthalmic delivery of curcumin. Colloids Surf B Biointerfaces 2015;128:322-30.

[16] Calfrs J, Edsman K, Peterson R. Rheological evaluation of23. Hoffmahydrog from aPoloxamer as an in situ gel for ophthalmic use. Eur J Pharm Sci., 6, 2000, 105.

[17]Rathore KS, Nema RK. Formulation & evaluation of 24. Hong- 222.ophthalmic films for timolol maleate. Planta indica, 4, 2008, 49-50.

[18] Gurny R, Ibrahim H, Buri P. The development & use of in situ formed gel triggered by ph. In Biopharmaceutics of ocular solutioRelease drug delivery. ed. Edman, 1993, 81-90.

[19] S. Cohen, E. Lobel, A. Trevgoda, Y. Peled. A novel in situ- forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. J. Control. Release. 44, 1997, 201-208.

[20] B. Srividya, R.M. Cardoza, P.D. Amin. Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. J. Control Release., 73, 2001, 205-211.

[21]Wen-Di Ma, Hui Xu, Chao Wang, Shu-Fang Nie, Wei-San Pan, 28. Shastrideliver Pluronic F127-g-poly(acrylic acid) copolymers as in situ gelling vehicle for ophthalmic drug delivery system, int. j. of pharmaceutics, (350), 2008, 247-256.

[22] Sirish vodithala, Sadhna Khatry, Nalini Shastri, M. Sadanandam, Formulation and evaluation of ion activated

[23] Jothi M, Harikumar SL and Geeta Aggarwal, In-situ ophthalmic gels for the treatment of eye diseases, International Journal of Pharmaceutical Sciences andResearch, 3, 2012, 18911904.

[24]Rajas NJ, Kavitha K, Gounder T, Mani T, In-Situ ophthalmic gels a developing trend, Int J Pharm Sci Rev and Res, 7, 2011,

[25] Malavade S. Overview of the ophthalmic system. In: Pathak Y, Sutariya V, Hirani AA, editors. Nano-Biomaterialsfor ophthalmic drug delivery. Springer International Publishing: 2016. p. 9-35.

[26]. Cohen S., Lobel E., Trevgoda A., Peled Y. A novel in-situ forming Ophthalmic drug delivery system from alginates undergoing gelation in the eye. Journal of Controlled Release., 44, 1997, 201-208.

[27]Grant G.T., Morris E.R., Rees D.A., Smith P.J.C., Thom D. Biological interactions between polysaccharides and divalent cations: The egg box model. FEBS Lett., 32, 1973, 195-198.

[28]. Al-Shamklani A, Bhakoo M, Tuboku MA, Duncan R.Evaluation of the biological properties of alginates

[29]Roopa Rani K. Formulation and invitro evaluation of fluvasatin in-situ gels. Introduction.IJCRR [Internet], 2023; 22(01): 1367-87. Available from: http://ymerdigital.com