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# *In situ* Gel forming Povidone Eye Drop

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**ABSTRACT:** Eye is a delicate organ of the body whose defence mechanism restricts entry of exogenous substances. Conventional drug delivery systems get washed off within a short period of time and result in poor contact time and ocular bioavailability. PVP iodine is an effective antibacterial agent with broad antibacterial and antiviral spectrum and no bacteria resistance. Purpose of the current study is to prolong the contact time of PVP iodine in the ocular using a suitable carrier such as *in situ* gel, which can effectively deliver the drug for an extended duration of time hence not only reduce the systemic side effects but also improve the therapeutic efficacy, patient compliance. Development of *in situ* gel having protracted ocular residence time is one of the milestone triumphs by pharmaceutical researchers for treatment of eye ailments. The development of in situ gel systems has received significant interest from ophthalmologists over the past few years. *In situ* gel forming systems have shown their potential in increasing the residential time because of bio-adhesiveness of formed gel.

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## INTRODUCTION:

The ocular drug delivery system is considered as crucial and challenging as the human eye is an isolated organ where the delivery of drugs is quite difficult. Moreover, the conventional ophthalmic formulations exhibit a short precorneal residence time and poor bioavailability due to rapid and extensive elimination of drugs from precorneal lachrymal fluid by solution drainage, lacrimation, and non-productive absorption by conjunctiva [1]. In order to surpass the drawbacks associated with the conventional ophthalmic formulations, various attempts have been made towards the development of stable sustained release *in situ* gels. Newer research in ophthalmic drug delivery systems is directed towards incorporation of several drug delivery technologies, that includes to build up systems which not only extend the contact time of the vehicle at the ocular surface, but which at the same time

slow down the elimination of the drug. *In situ* gel system is formulated as liquid preparation suitable to be instilled into eyes which upon exposure to the physiological environment changes to gel, thus increasing the precorneal residence time of the delivery system, and enhances the ocular bioavailability of the drug [2].

*In situ* gel systems refer to a class of novel delivery vehicle; composed of natural, semi synthetic or synthetic polymers, which present the unique property of sol to gel conversion on receipt of biological stimulus [3]. The most critical challenge of today's health care is the timely liberation of therapeutics to their specific target in a safe, reproducible and patient-compliant manner. As for conventional therapy is concerned, regardless of the route of administration, drug molecules on their way from the point of administration to their pathological target are continuously challenged by multiple physiological barriers such as enzymatic degradation of drug molecule in the stomach, absorption across intestinal epithelium, hepatic clearance, short plasma half-life and nonspecific tissue distribution [4]. *In situ* gels deserve special mention as they provide a lucrative approach for ocular drug delivery, which is comparable with both conventional and novel approaches for ocular delivery. *In situ* gel systems comprise delivery vehicles composed of the polymers (natural, semi synthetic or synthetic) with the unique property of sol to gel conversion when influenced by biological stimulus. This in imitable property of sol to gel conversion provides various advantages to these systems such as;

- Easy administration like a conventional eye drop formulation.
- Reproducible and accurate dosing.
- Ease of fabrication.
- Prolonged retentively at the site of action.
- Sustained drug release due to a gel network formed after being influenced by the physiological stimulation.
- Easy scale-up and sterilization.
- Ease of system engineering in a combinatory approach (by choosing polymers with multiple function penetration enhancer/ Mucoadhesion/ *in situ* gel property) [5-7].

Drug delivery to ocular mucosa for local treatment is associated with great possibilities, but often also with many obstacles. The physiological constraints imposed by the protective mechanisms of the eye lead to low absorption of drugs. The most common way to deliver drugs to the eye is to instill an aqueous solution of the drug into the eye. The bioavailability of a drug introduced in this way is often very low, typically < 5 %, depending on its physicochemical properties. Such low bioavailability is attributed to extensive precorneal drug loss by nasolacrimal drainage. The rapid elimination of the instilled drug often results in a short duration of therapeutic effect and, consequently, the need for a frequent dosing regimen [7].

Ocular therapy would be significantly improved if the precorneal residence time of the drug could be increased. The best way of doing so is by designing *in situ* gel-forming drug delivery systems that are conveniently administered into the eye as a liquid; where after, they undergo a transition into a gel brought about by the presence of stimuli-responsive polymers.

An *in situ* gel-forming solution delivery system combines the advantages of a solution, being patient convenient, with the favorable residence time of a gel. Due to the viscoelastic properties, these gels resist ocular drainage leading to longer contact times and duration of action. Parameters that can change and trigger this sol-gel phase transition include pH or temperature or ionic strength of the tear fluid. Numerous types of stimuli-responsive polymers used in ocular drug delivery systems have been reviewed previously [8]. Of all these systems, gellan gum-based *in situ* gel systems have been shown to significantly prolong the ocular contact time of the drug in animal and human studies [9].

Povidone-iodine is a commercially available iodophor routinely used in ophthalmology and general surgery. Povidone-iodine solutions have been proven effective before (5 % solution) [10,11] and after ocular surgery(1.25 %) [12,13], at birth (2.5 %), [14] and for active infections (1.25 %) [15]. PVP-I is the only agent known to prevent post- op endophthalmitis. Solutions of PVP-I are toxic to viruses (including HIV), fungi, parasites and bacteria with no known development of resistance. It is well described in the literature that aqueous PVP-I solutions exhibit greater antiseptic efficacy at lower concentrations [16]. Furthermore, these lower concentrations are less irritating to the eyes, ears and skin. A 0.6 % PVP-I in combination with dexamethasone formulation is advancing into Phase III clinical trials by Shirein March 2017 [17, 18]. PVP iodine and their preparation are official in USP, European pharmacopoeia and are recognized as effective broad spectrum biocidal agents [19]. The *in vitro* biocidal activity has been studied for years against bacteria, yeast, moulds, viruses, fungi, protozoa, actinomycetes

and rickettsia [20,21]. PVP iodine ophthalmic solution in dose of one drop three times a day has been administered in the first postoperative week. It controls the increase in conjunctival bacterial colony-forming units [22]. Unlike the other agents currently used for prophylaxis against *Ophthalmia neonatorum*, PVP iodine is also effective against microorganisms other than bacteria. PVP iodine has been found to be potent against fungi in concentrations as low as0.1 % [23]. According to properties of PVP iodine, it is suitable for the prophylaxis and treatment of ophthalmia neonatorum. In their pilot study, Isenberg and his associate have shown that a 2.5 % solution of PVP-iodine was not irritating to the sensitive eyes of neonates, whereas a 5.0 % solution that they had used in previous studies occasionally produced some conjunctival hyperemia [24]. In contrast to silver nitrate and erythromycin, PVP iodine has not been associated with true bacterial resistance. PVP iodine is highly effective against the bacteria found in the eye at the birth. Although silver nitrate, erythromycin and PVP iodine reduce the number of colony forming units, PVP iodine achieves the best level of statistical significance and erythromycin was shown to be the worst [25]. In Isenberg clinical study thyroid disorders did not develop in any of more than 3000 newborns that received a 2.5 % ophthalmic solution of PVP iodine [23].

## ANATOMY AND PHYSIOLOGY OF THE EYE:

In ocular delivery, the physiological constraints imposed by the protective mechanisms of the eye, like short precorneal residence time of the solutions due to constant lacrimal drainage usually results in low absorption of drugs and, consequently, a short duration of the therapeutic effect. The faster washing by tear fluid in response to the body's reflex defense mechanism also results in frequent administration. Moreover, systemic absorption of the drug drained through the nasolacrimal duct may result in some undesirable side. Among the factors that limit ocular absorption is the relatively impermeable nature of the corneal barrier. Nevertheless, the barrier also serves to reduce undesired systemic absorption and side effects associated with many drugs. The cornea consists of three membranes, the epithelium, the endothelium, and inner stroma which are the main absorptive barriers (Fig 1). The epithelium composed of lipophilic cellular layers acts as a barrier to ion transport. The tight junctions of epithelium serve as a selective barrier for small molecules and prevent diffusion of macromolecules via the Para cellular route.

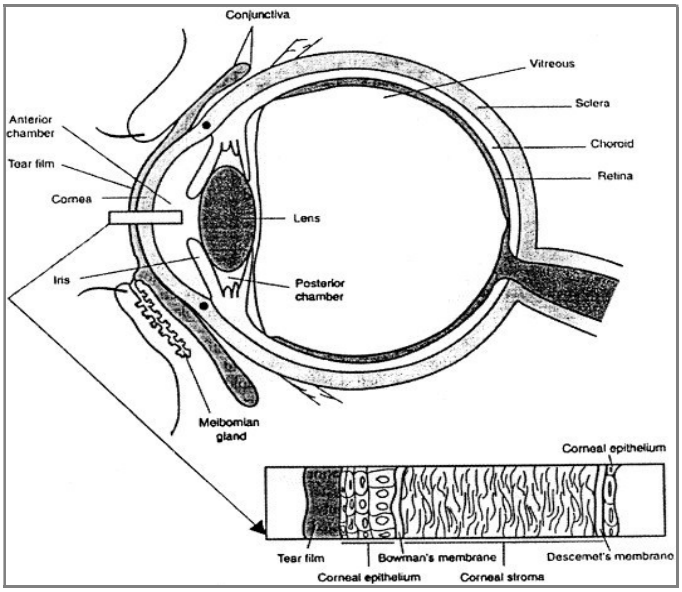


**Fig 1. Schematic representation of the human eye.**

The stroma beneath the epithelium is a highly hydrophilic layer making up 90 % of the cornea. The more lipophilic the drug is, the more resistance there is to cross the stroma and the more hydrophilic a drug, the more resistant the transport across the epithelium. Hence, physicochemical drug properties, such as lipophilicity [26], solubility [27], and molecular size and shape [28], and charge and degree of ionization [29] affect the route and rate of permeation in the cornea.

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The basis of this can be found in the anatomical arrangement of surface tissues and in the permeability of the cornea. Topical administration is usually referred over systemic administration for the treatment of eye diseases, and topically applied drugs should reach the inner parts of the eye to elicit the response. However, effective tear drainage and blinking results in a 10-fold decrease in drug concentration when the drug solution is administered in the form of drops, which results in a very short period for which the drug has access to the ocular tissues [30-32].

The major route for drug absorption in ocular drug delivery is through transcorneal penetration. However, any drug molecule administered by the ocular route has to cross the precorneal barriers, tear film, and the conjunctiva before achieving the anatomical barrier of the cornea. These precorneal barriers slow the penetration of active ingredients into the eye. Tear production, a protective physiological mechanism, reduces the effective concentration of a drug in contact with the cornea due to increased spillage, dilution of the

drug, accelerated clearance, and binding of the drug molecule to the tear proteins. The buffering action of the carbonic acid and weak organic acids present in tears also affect the extent of ionized and non-ionized forms of the drug and hence its bioavailability. The conjunctiva of the eyelids and globe is a thin, vascularized mucus membrane, which is involved in the formation and maintenance of the tear film and in the protection of the eye [33,34].

The cornea is the major route by which most ophthalmic drugs enter the eye. Corneal epithelium, stroma, and endothelium are the main absorptive barriers of the cornea and their relative thick-nesses are about 0.1:1.0:0.01, respectively. Most of the ocular drugs penetrate the cornea by diffusion. The paracellular and transcellular pathways are two other mechanisms for drug transport across the cornea [35].

The corneal epithelium is rich in lipids and its poor permeability to non-lipophilic/ ionized drug substances and the differential penetration of nonionized forms is due to the desquamated cells on the surface layers. In the case of ionized molecules, not only the degree of ionization but also the charge of the molecule affects their corneal penetration. The epithelium is reported to be the rate-limiting barrier to transcorneal transport. The stroma and the endothelium play significant roles for smaller lipophilic molecules. The corneal stroma is composed of collagen and allows the hydrophilic molecules to pass through easily due to its highly hydrophilic, porous, and open knit structure; however, it provides a greater barrier for macromolecules [36, 37].

The corneal endothelium is a single-cell layer permeable to lipid soluble materials and almost impermeable to ions due to its rich phospholipid content. For most topically applied drugs, passive diffusion along their concentration gradient, either transcellular or paracellular, is the main permeation mechanism across the cornea. In contrast, the cornea1 transport of L-lysine involves the Na+-K+-ATPase pump and requires a stereo specific carrier-mediated transport system [38]. To date, pharmaceutical technologists have tried various approaches to increase the bioavailability and duration of the therapeutic action of ocular drugs. The first approach was based on use of drug delivery systems like ocular inserts, collagen shields, and implants that provide controlled and continuous delivery of the drug. The second approach involved the use of liposomes, nanoparticles, and penetration enhancers to maximize the corneal drug absorption and minimize the precorneal drug loss. Although these systems were superior to conventional ocular formulations, they were found to have numerous limitations, which encouraged researchers to attempt novel ocular drug delivery systems that will not only increase the ocular bioavailability of the drug, but will also, provide controlled and continuous delivery for a prolonged period of time. Thus, researchers developed *in situ* gel forming systems that were found to promote precorneal retention, along with administering accurate and reproducible quantities compared to already gelled formulations (Fig 2) [39].

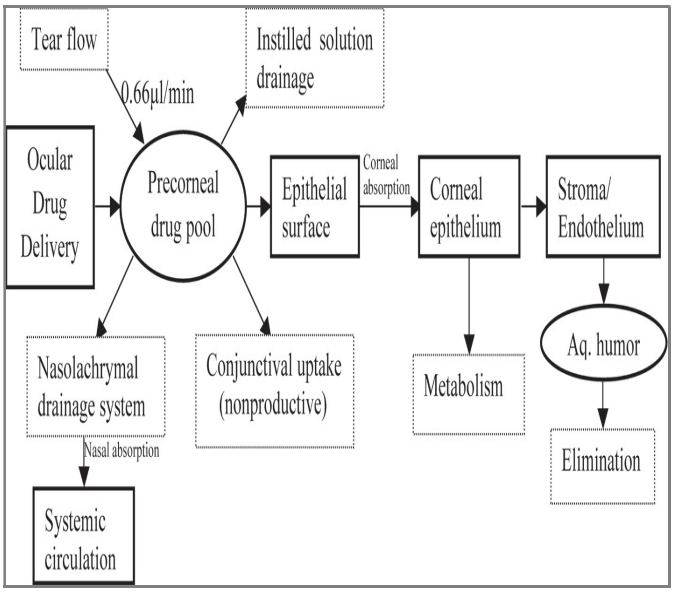


**Fig 2. Model depicting precorneal and intraocular drug dispositioning.**

## *IN SITU* GELLING SYSTEM:

*In situ* gel forming systems are drug delivery systems that are in solution form before administration in the body but once administered, undergo gelation *in situ*, to form a gel triggered by external stimulus such as temperature, pH and release the drug in sustained or controlled manner. This novel concept of producing *in situ* gel was suggested for the first time in the early 1980s. Gelation occurs via the cross-linking of polymer chains that can be achieved by 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 undergo phase transition in the conjunctival cul-de-sac to form viscoelastic gels due to conformational changes of polymers in response to the physiological environment. 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 [40]. Both natural as well as synthetic polymers can be used for the fabrication of *in situ* gels (Fig 3) [41].

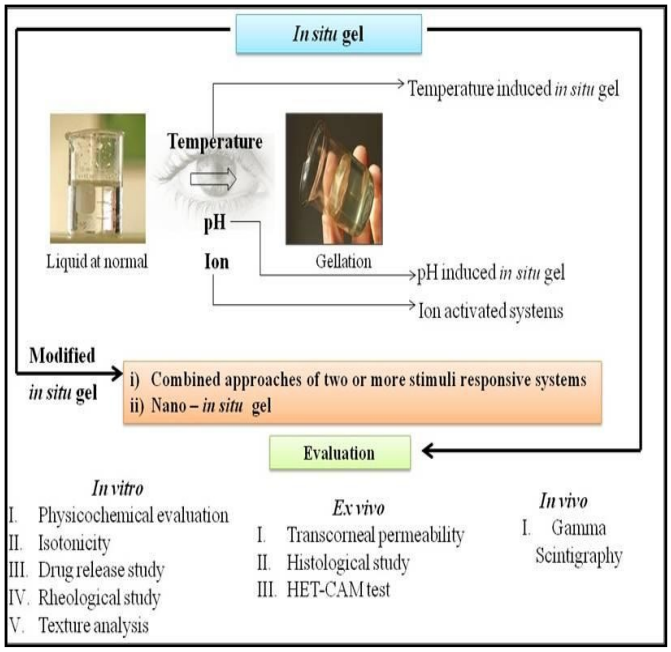


**Fig 3. Overview on *in situ* gel.**

**IDEAL PROPERTIES FOR *IN SITU* FORMULATIONS [42,43]:**

- Physical state: Formulation should be free flowing liquid which allows ease of administration with reproducible dose delivery.
- Phase transition: Upon installation it should undergo sol-to-gel formation by phase transition.
- Strength of gel: Formed gel should be strong enough to withstand the shear force in cul-de-sac which prolongs residence time of drug.

## *IN SITU* GEL-FORMING SYSTEMS FOR OCULAR DRUG DELIVERY:

From the point of view of patient acceptability, a liquid dosage form that can sustain drug release and remain in contact with the cornea of the eye for extended periods of time is ideal. If the precorneal residence time of a drug could be improved only modestly, then improved local bioavailability, reduced dose concentrations, less total drug dose, improved patient acceptability, and reduced dosing frequency may result. Therefore, delivery systems based on *in situ* gel-formation offer an attractive alternative. Such systems involve a phase transition in which the installed gels upon reaching the cul-de-sac of the eye. Therefore, these systems offer the dual advantage of an easy to administer liquid formulation along with the increased residence time of a gel.

Parameters that can change and trigger the phase transition of *in situ* gels include pH, temperature, and ionic strength [44,8]. Literature examples of some of the polymers used in *in situ* gel systems that employed one or more of these phase change mechanisms include the following:

- Gelling triggered by a change in pH - CAP (cellulose acetate phthalate) latex, cross linked polycarbophil acid and its derivatives such as carbomers and polycarbophil [46,39].
- Gelling triggered by temperature change - Poloxamer, methyl cellulose, and Smart Hydrogel™ [46-48].
- Gelling triggered by change in ionic strength – Gel rite (gellan gum) and alginate [49-51].
- Combination system with a thermally-induced gelling material (methyl cellulose) and pH-induced gelling material (carbomer) was also used to achieve *in situ* gelling properties with less total polymer content [52].
- In all of the above systems, a polymer is used as the gelling system. Many high molecular weight polymers with different functional groups (such as carboxyl, hydroxyl, amino, and sulfate) capable of forming hydrogen bonds, yet not crossing biological membranes, have been screened as possible excipients for *in situ* gel-forming ocular delivery systems [53,8].

## POLYMERS FOR *IN SITU* GEL-FORMING DRUG DELIVERY SYSTEMS:

### Ideal characteristics of polymers:

The polymers used for in-situ gelling systems should have following characteristics [54];

- It should be biocompatible.
- It should be capable of adherence to mucus.
- The polymer should be capable of decreasing viscosity with increasing shear rate there by offering lowered viscosity during blinking and stability of tear film during fixation.
- It should have pseudo plastic behaviour.
- It should be tolerable.
- It should have good optical activity.
- It should influence the tear behaviour.

### Cellulose derivatives:

A number of substituted cellulose-ethers have been employed for artificial tear solutions and as viscosity-

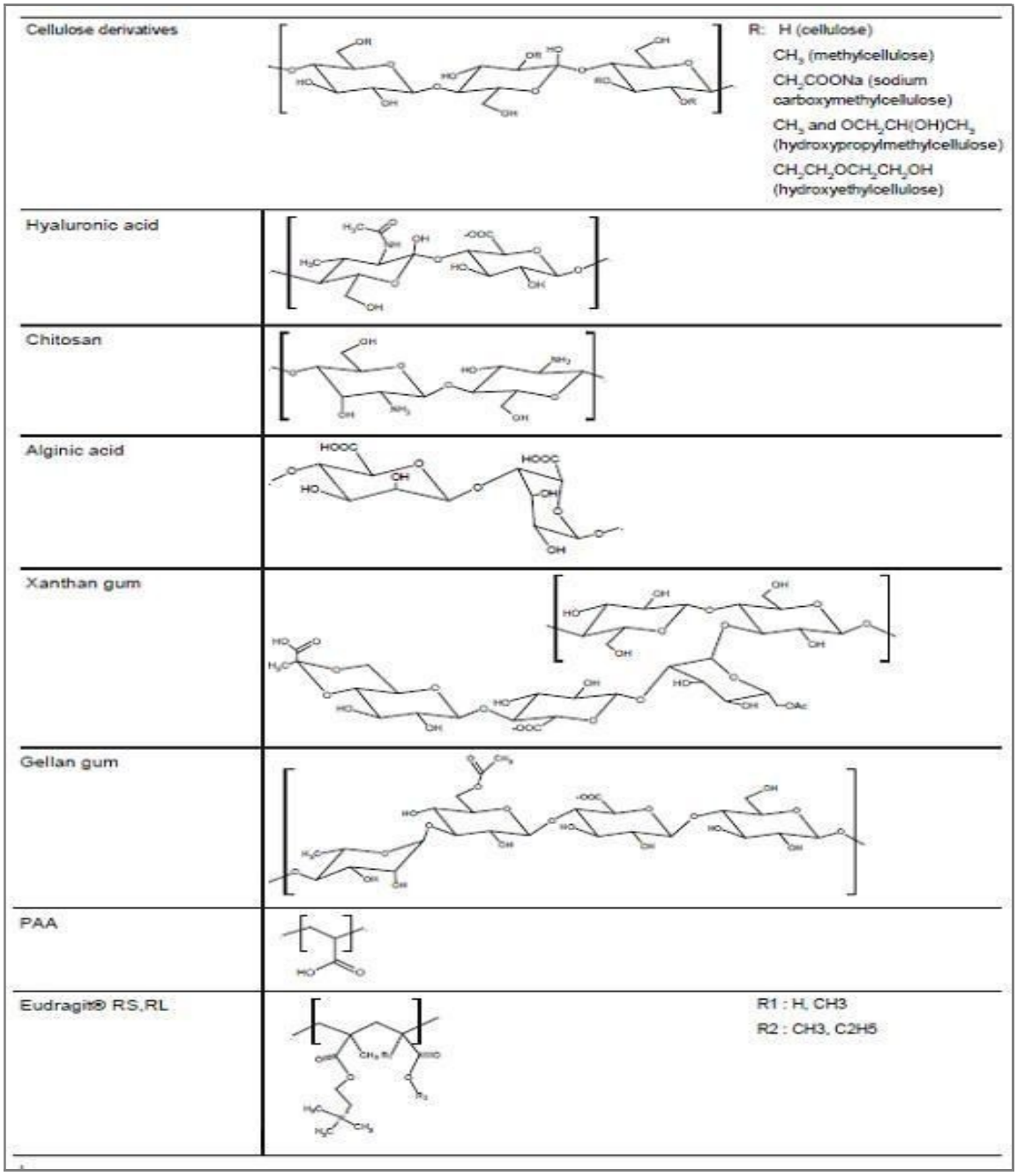


**Fig 4. Structures of various polymers.**

enhancing ophthalmic vehicles [55]. Methylcellulose also possesses wound-healing properties and is a suitable tear substitute for dry eyes, especially for those with punctate lesions [56]. All cellulose-ethers impart viscosity to the solution and they have wetting properties and increase the contact time by virtue of their film forming properties. Some cellulose-ethers (e.g. hydroxy propyl methylcellulose and hydroxypropyl cellulose) also exhibit surface active properties, interact with components of the tear film, and alter the physicochemical parameters governing the tear film stability [57]. Surface active viscosifying agents can influence the blinking rate, which in turn influences the elimination of the drug instilled. They cause irritation and extensive lacrimation, provoking a rapid wash out of the ophthalmic solution and, consequently, a poor bioavailability. Generally, less surface active hydroxyethyl cellulose is better tolerated, but the mucoadhesive properties of non-ionic cellulose-ethers are rather poor [58,59]. However, sodium Carboxymethyl cellulose (Na CMC) exhibits a mucoadhesive capacity comparable to that of poly (acrylic acid - PAA) (Fig 4) [39].

**Acrylates:**

The mucoadhesive properties of poly (acrylic acid) are due mainly to hydrogen bonding, while hydrophobic

interaction with mucin is not significant [60]. When anionic polymers interact with mucin, the maximum interactive adhesive force occurs at an acidic pH, suggesting that the mucoadhesive polymer in its protonated form is responsible for the Mucoadhesion. The swollen polymer entangles with mucin on the eye surface, stabilizing a thick hydrogel structure [61]. Polyanionic polymers, such as polyacrylate or carbomers, were proposed as long-lasting artificial tears for the relief of dry eye syndrome and traumatic injury. The use of these high molecular weight polymers is based on inherent mucus-like and lubricating properties, shear thinning behaviour, and good retention on the ocular surface [62,63]. To enable the controlled release of drugs with low solubility, Setiawan and colleague's synthesized poly (acrylic acid)–cyclodextrin conjugates (Carbopol 934P: hydroxypropyl-beta-cyclodextrin). When administered to the eye, an increase in the bioavailability of the drug complexed with cyclodextrin can be obtained. Moreover, after installation, the preparation forms a gel. In rabbits, the aqueous humor bioavailability (as determined by the area under the concentration time profile over the first 3 h) of hydrocortisone 0.3 % (w/v) in the new delivery system was 6-fold higher than for the suspension. A similar increase was observed for the cornea and the iris/ ciliary body bioavailability.

**Hyaluronan:**

Besides synthetic polymers, natural macromolecules such as hyaluronan (HA), present in the vitreous body of the eye, were proposed as viscosifying agents. Sodium hyaluronate molecules have physical properties and a composition comparable to tear glycoproteins and easily coats the corneal epithelium. Polymers adsorbed at the mucin/aqueous interface extend into the adjacent aqueous phase, thereby stabilizing a thick layer of water. The non-Newtonian behaviour of sodium hyaluronate combines the advantage of high viscosity at rest between blinks with those of lower viscosity during blinking [64, 65].

Diluted solutions of sodium hyaluronate have been employed successfully as tear substitutes in severe dry eye disorders. The beneficial effects are attributed to the viscoelasticity, biophysical properties similar to mucins, which provide a long-lasting hydration and retention. Moreover, good lubrication of the ocular surface is obtained [66, 67]. Hyaluronic acid is an important constituent of the extracellular matrix and may play a role in inflammation and wound healing and may promote corneal epithelial cell proliferation. Gurney and colleagues confirmed the positive influence of hyaluronate vehicles on the bioavailability of pilocarpine. High molecular weight of the polymer is an essential requirement for the prolonged precorneal residence time of the preparation [69].

**Chitosan:**

The chitosan polymer is biodegradable, biocompatible and non-toxic. It possesses antimicrobial and wound-healing properties. Moreover, chitosan exhibits a pseudo plastic and viscoelastic behavior [70-72]. The mucoadhesive properties of chitosan are determined by the formation of either secondary chemical bonds such as hydrogen bonds or ionic interactions between the positively charged amino groups of chitosan and the negatively charged sialic acid residues of mucins, depending on environmental pH [73]. The mucoadhesive performance of chitosan is significantly higher at neutral or slightly alkaline pH as in the tear film. Only in the presence of an excess of mucin, does a strengthening of the mucoadhesive interface occur [74]. A 3-fold increase of the precorneal residence time of tobramycin was achieved when adding chitosan to the formulations, compared to the commercial solution of the drug. Only a minimal influence was observed from the concentration and molecular weight of chitosan employed, indicating a saturable bioadhesive mechanism based on ionic interactions of the cationic polymer with the negative charges of the ocular mucus [75].

**Thiomers:**

Thiolated polymers, or so called thiomers, are capable of forming covalent bonds with cysteine-rich sub-domains of mucins. The extensive cross-linking process of the thiomers with mucins resulted in a tremendous increase in viscosity and Mucoadhesion independent of pH or ionic strength of the medium. The mucoadhesive properties of a chitosan thioglycolic acid conjugate and a poly(acrylic acid)–cysteine conjugate improved 10-fold and even 100-fold, respectively, compare to the native polymers [76,77].

**Polysaccharides:**

Besides chitosan, numerous polysaccharides were evaluated as mucoadhesive ophthalmic vehicles: polygalacturonic acid, xyloglucan, xanthan gum, pullulan, scleroglucan, and carrageenan [78-81]. Also, in the case of polysaccharides, the formation of

macromolecular ionic complexes with drugs improved the bioavailability and lengthened the therapeutic effect when compared to drug solutions. Toxicological studies indicate that xyloglucan is very well tolerated by conjunctival cells, has cell protective properties, and is able to reduce drug-related toxicity (e.g. fluoroquinolones, timolol, Merthiolate) probably due to its mucin-like structure. Xyloglucan might promote wound healing depending on its influence on the integrin recognition system [82,83]. Timolol, in association with xyloglucan, has a prolonged duration of action and is suitable for ocular administration in cases of elevated intraocular pressure. In rabbits, high timolol concentrations in the ocular tissues were measured, but with low systemic absorption [84].

**Gellan gum:**

Among all *in situ* gel-forming systems, systems that function upon activation by change in ionic strength using gellan gum are most effective. These systems overcome the drawbacks associated with other systems where phase transition is mediated by pH and temperature. In the former case, a highly acidic pH could result in ocular irritation and temperature fluctuations during storage could affect gelation and the inevitable need of high polymer contents.

Gellan gum is an exocellular microbial hetero polysaccharide that is secreted by the strain *Pseudomonas elodea,* an interest to the food and pharmaceutical industries. Chemically, it is an anionic polymer with a high molecular weight (approx.5 × $10^5$daltons, deacetylated). The polymer is stable to both heat and pH (pH 3.5-10.0) [85]. Native gellan gum consists of a backbone of repeating unit of ß-1,3-D-glucose, ß-1,4-D-glucuronic acid, ß -1,3-D-glucose, α-1,4-L-rhamnose,and the two acyl groups, acetate and glycerate, bound to a glucose residue adjacent to glucuronic acid. The acetyl groups in native gellan gum are removed by alkaline treatment to produce deacetylated gellan gum (Fig 4).

**CARBOPOL:**

It is a pH sensitive polymer. It is also called carbomers and acrylic acid polymer [86]. Carbopol is a high molecular weight, cross linked polyacrylic acid derivative and has the strongest mucoadhesive property. It is a water soluble vinyl polymer. It shows sol to gel transition, in aqueous solution, when the pH is raised above its pKa value of about 5.5. As the concentration of carbopol increases, its acidic nature may cause irritation to the eye. Addition of cellulose will reduce polymer concentration and will also improve gelling property. The Mucoadhesive property of carbopol is due to our mechanisms of interaction between mucin and poly (acrylic acid)-electrostatic interaction, hydrogen bonding, hydrophobic interaction and inter diffusion [87]. Carbopol molecule is tightly coiled acidic molecule. Once dispersed in water, the carboxylic group of the molecule partially dissociates to form a flexible coil. Being a pH sensitive polymer, increase in solution pH results in swelling of the polymer. In an acidic medium, it is in a collapsed state due to hydrogen bonding, as the pH increases, electrostatic repulsion occurs between the anionic groups, resulting in gel swelling. The gelling effect is activated in two stages: dispersion and hydration of Carbopol, neutralizing the solution by addition of sodium hydroxide, Triethanolamine, or potassium hydroxide (Fig 5) [88].

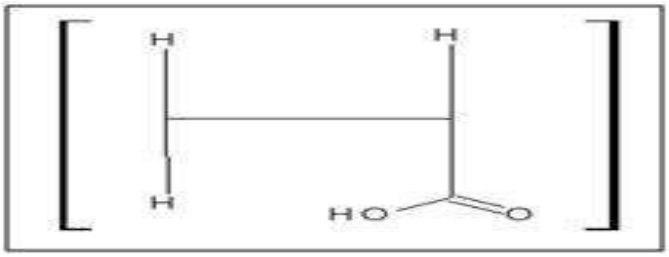


**Fig 5. Structure of Carbopol** [88].

**POLOXAMER:**

It is a temperature sensitive polymer. It is commercially called Pluronic. It is a water soluble tri-block copolymer consisting of two polyethylene oxide (PEO) and polypropylene oxide (PPO) cores in an ABA configuration. Polypropylene oxide is the hydrophobic central part which is surrounded on both sides by hydrophilic Polyethylene Oxide. It has good thermal setting property and increased drug residence time. It gives colorless, transparent gel. Concentrated aqueous solutions of Poloxamer form thermo reversible gels [87]. At room temperature (25 ºC), Poloxamer behaves as viscous liquid and is transformed to transparent gel when temperature increases (37 ºC). At low temperature, it forms a small micellar subunit in solution and increase in temperature results in an increase in viscosity which leads to swelling to form large micellar cross linked network (Fig 6).

**SODIUM ALGINATE:**

It is anion-sensitive polymer. It is also known as algin, alginic acid, sodium salt, E401, Kelcosol, Keltone, Protanal, sodium polymannuronate [86].

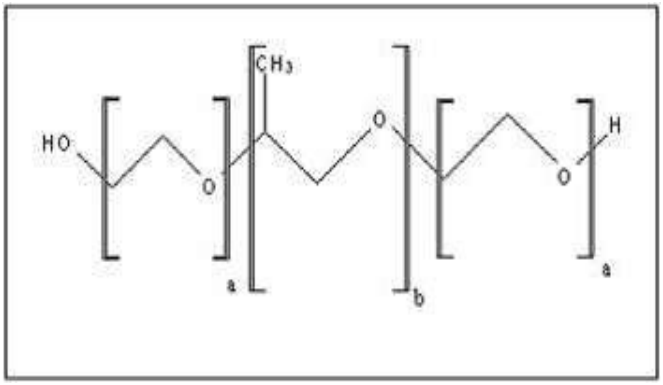


**Fig 6. Structure of Poloxamer.**

Sodium alginate is a gum extracted from brown algae. It is a salt of alginic acid. It is a linear block polysaccharide consisting of two types of monomers-β-D-Mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. It exhibits good mucoadhesive properties due to the presence of carboxylic groups. It is biodegradable and non-toxic. It has a high molecular weight of 20 to 600kDa [89]. The monomers of alginate (β-D-Mannuronic acid (M) and α-L-glucuronic acid (G) are arranged as M-M blockor G-G block with alternating sequence (MG) block. Upon interaction of G block of polymer with calcium moieties, formation of homogeneous gel takes place. Mechanical strength and porosity of hydrogel depends on G: M ratio, type of crosslinker used and concentration of alginate solution (Fig 7) [88].

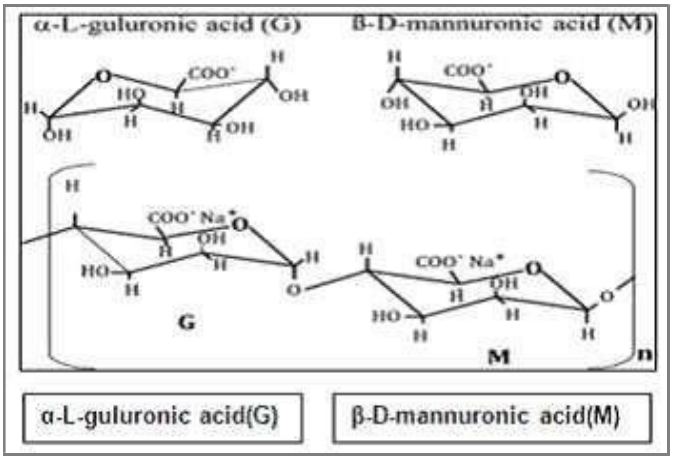


**Fig 7. Structure of Sodium Alginate.**

**Hydroxypropyl Methyl Cellulose (HPMC):**

It is a temperature sensitive polymer. It is also known as Hypromellose and Methocel [86]. It is water soluble cellulose ether [90]. Widespread acceptance of HPMC due to [91] solubility characteristics of the polymer inorganic and aqueous solvent system. Non-interference with drug availability. Flexibility and absence of taste and odor. Stability in the presence of heat, light, air or reasonable levels of moisture (Fig 8).

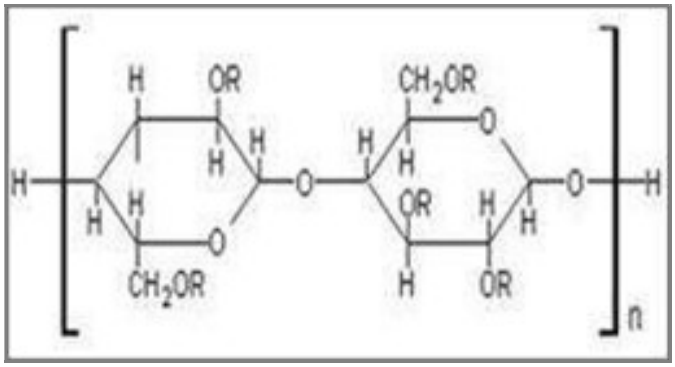


**Fig 8. Structure of HPMC [88].**

At low concentrations (1 to 10 wt. %) aqueous solutions of HPMC are liquid at low temperature but gel upon heating [92]. It shows phase transition between 75 and 90ºC. These phase transition temperatures can be lowered by chemical or physical modifications [92]. By reducing the hydroxyl propyl molar substitution of HPMC, its transition temperature can be lowered to 40 ºC. Gelation of HPMC solutions is primarily caused by the hydrophobic interaction between molecules containing methoxy substitution. At low temperatures, the macromolecules are hydrated, and there is little polymer-polymer interaction other than simple entanglement. As the temperature is raised, the polymers gradually lose their water of hydration, which is reflected by a decline in relative viscosity. Eventually, when sufficient but not completed hydration of the polymer occurs, polymer–polymer associations take place, and the system approaches an infinite network structure, as reflected experimentally by a sharp rise in relative viscosity. This sol-gel transformation has been exploited to design *in situ* gelling systems. These systems exhibited low viscosity at 23 °C and formed soft gels at 37 ºC.

**Xyloglucan:**

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod-like chains. The sol-gel transition temperature varies with the degree of galactose elimination. Gelation is possible only when the galactose removal ratio exceeds 35 % [93,94].

## VARIOUS APPROACHES OF *IN SITU* GELATION:

Various approaches used for *in situ* gelling systems are Stimuli-responsive *in situ* gel system, temperature induced *in situ* gel system, pH induced *in situ* gel system, chemically induced *in situ* gel system, Ionic cross linking (Ion activated systems) and Enzymatic cross linking.

### Stimuli responsive *in situ* gel system:

Polymers used in stimuli responsive system are also known as stimuli-sensitive, intelligent, smart or environmentally sensitive polymer. These polymers adapt small external changes in environment and undergo relatively large and abrupt, physical or chemical changes [95]. These polymer systems may recognize a stimulus as a signal and then change their chain conformation in direct response [96].

### Temperature induced *in situ* gel system:

Temperature- sensitive systems are the most commonly studied class of stimuli responsive polymer systems for ocular targeting [28]. The use of a biomaterial whose transitions from sol to gel is triggered by change in temperature is an attractive way to achieve *in-situ* formation [97]. The ideal phase transition temperature for this type of systems is physiologic temperature where there is no need of external source of heat other than that of body for gelation. For convenience, temperature-sensitive *in situ* gels are classified into negatively thermo-sensitive, positively thermo-sensitive, and thermally reversible gels [98].

**Table 1. Composition of temperature induced formulation.**

| Sl. No. | Ingredients | FF1 (mg) | FF6 (mg) | FF (mg) |
|---|---|---|---|---|
| 1 | PVP iodine | 0.25 | 0.25 | 0.25 |
| 2 | Pluronic18 | 15 | 15 | 15 |
| 3 | Carbomer934 | - | 0.03 | 0.04 |
| 4 | Triethanol-amine | q. s. | q. s. | q. s. |
| 5 | Cold DW | 10 ml | 10 ml | 10 ml |

**q.s. – Quantity sufficient. DW – Distilled water.**

Negative temperature-sensitive *in situ* gels have a lower critical solution temperature (LCST) and contract upon heating above the LCST. A positive temperature sensitive *in situ* gel has an upper critical solution temperature (UCST) and contracts upon cooling below the UCST [40,41]. Formulation is liquid at room temperature (20 to 25°C) which undergoes gelation in contact with body fluid (35 to 37 °C). Temperature increases degradation of polymer chains which leads to formation of hydrophobic domains and transition of an aqueous liquid to *in situ* gel [99]. Poloxamer, Xyloglucan, Chitosan and naturally occurring cellulose derivatives are most commonly used polymers in preparation of thermo sensitive *in situ* gelling system (Table 1).

### pH induced *in situ* gel system:

Sol to gel phase transition is achieved by change in pH. All pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of *in situ* gel increases as external pH increases in case of weakly acidic (anionic)groups, but decreases if polymer contains weakly basic(cationic)groups. Most of anionic pH-sensitive polymers are based on PAA (Carbopol, carbomers) or its derivatives. Sol to gel transition occurs when pH rises from 4.2 to 7.4. At higher pH polymer forms hydrogen bonds with mucin which leads to formation of *in situ* gel [100]. 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 [101].

### Ion activated systems:

Ion activated gelling system is triggered by cations present in eye tear fluid like $Na^{+}$, $Ca^{+2}$ and $Mg^{+2}$. Generally anionic polymers are used in the formation of ion sensitive drug delivery system. Polymers like sodium alginate, gelrite, tamarind gum, gellan gum are used in combination with other polymers like MC and HPMC to increase the effect. They provide sustain release of drug by providing mucoadhesivenes. This system based on the mechanism of ionic interaction of ions of polymer and divalent ions of tear fluid. As soon as anionic polymers come in contact with cationic ions they convert in to gel [100, 99]. The concentration of $Na^{+}$ in human tear is 2.6 g/l is particularly suitable to cause gelation of material when formulation administered topically [102].

## *IN-SITU* GEL EYE DROPS FORMULATIONS:

Deacetylated gellan gum (DGG) has temperature dependent and cation-induced gelation properties and a certain concentration of deacetylated gellan gum solution can form a moderate viscosity and strong water-

holding gel with the cations in the tears. Ophthalmological composition of the type which undergoes liquid-gel phase transition is shown in literature [103].

Addition of Povidone iodine (PVI), a few specific concentrations of deacetylated gellan gum based solutions could form gel *in-situ* (e.g. A formulation containing 0.45 % (w/w) deacetylated gellan gum), and the gel would change into the liquid form after adjusting to the surrounding pH. For solutions/formulations containing 0.3, 0.35 and 0.4 % (w/w) deacetylated gellan gum, their viscosities under the simulated physiological conditions were greater than those under non-physiological conditions, exhibiting typical *in-situ* gelling ability NaCl was selected as osmotic pressure regulator.

As DGG had anionic sensitivity characteristic, we considered adding a small amount of NaCl in the formulation, so it did not form a gel while under storage condition, but gel formation would be triggered by mixing with a small amount of tear fluid in conjunctival sac. Formulations containing PVP-I *in-situ* gel and NaCl of different concentrations were prepared according to Table 2. PVP-I *in-situ* gel eye drops and 0.3 % NaCl showed a weak gel state after standing for a period of time. The formulations would become liquid of low viscosity immediately after shaking slightly, making them ideal candidates for gelling.

Thermo reversible gels were prepared using cold technique [105]. The method involved slow addition of polymers in required quantities of cold distilled water further it was kept overnight for swelling. The polymer solution was taken in a beaker stirred continuously using a magnetic stirrer until a uniform solution was obtained and it was kept at ambient temperature for 24 h. A small amount of triethanolamine was added to adjust the pH 6.5.

An appropriate amount of PVP iodine solubilized in distilled water with continuous stirring until a uniform drug solution was obtained. The detailed composition of prepared formulation is depicted in Table 2 [106].

**Table 2. Formulations of PVP-I *in-situ* gel eye drops[104].**

| | DGG | PVP-I | NaCl | pH |
|---|---|---|---|---|
| Formu-lation (G) | 0.2 | 0.6 | 0.3 | 5.0-5.5 |
| | 0.3 | | | |
| | 0.4 | | | |

**All values except pH are expressed in % w/w.**

## EVALUATION OF *IN-SITU* GEL EYE DROPS:

### *In vitro* dissolution:

PVP-I *in-situ* gel eye drops were prepared according to the formulations set out in Table2. The sample was measured precisely (about2ml) and then added into a vial of 22 mm outer diameter, followed by addition of 350 µL simulated tear fluid (STF) and mixing quickly. The mixture was covered with a topper and weighed precisely and recorded. Placed samples into an air shaker (34.5 °C, 120 rpm), balanced for 10 min, and added simulated tear fluid (pre-heated to 34.5 °C, 2ml)along the side-wall slowly, took out all of the release medium at a different point in time, weighed quickly and recorded. About 10 min rebalance was needed after each shaking; take out the release medium before adding fresh STF (pre-heated to 34.5 °C); repeated this process until the gel was dissolved completely. Draw gel dissolution time curve by plotting the total amount of gel dissolution versus time (3n=3).

As results shown in Fig 2, PVP-I *in-situ* gel eye drops containing 0.2 % DGG (w/w) showed a good ability to retard tear erosion. There was still about 40 % of gel base that was not dissolved after 8 h of simulated tear fluid flushing. With the increase of concentration of deacetylated gellan gum, the dissolution of PVP-I *in-situ* gel eye drops became even slower, which effectively prolonged the residence time of PVP-I in the eye (Fig 9).

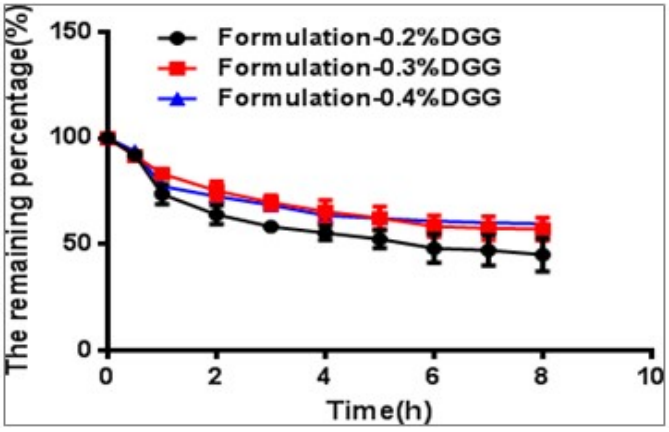


**Fig 9. The dissolution curve of PVP-I *in-situ* gel eye drops and DGG at different concentrations in STF.**

### *In vitro* release:

Took 2 ml PVP-I *in-situ* gel eye drops or 2 ml PVP-I normal saline solution, placed in a 14 KDa dialysis bag, added into 50 ml simulated tear fluid with pre-warmed to 34.5 °C, shook samples via air shaker at 120 rpm, took out the release medium STF every 30 min, and added fresh release medium (pre-warmed to 34.5°C)

quickly. Determined available iodine concentration by sodium thiosulfate titration (n=3), and calculated its accumulative release amount.

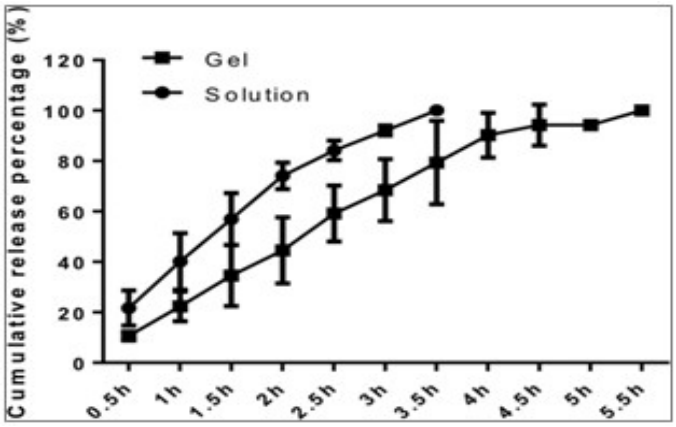


**Fig 10. *In vitro* cumulative release curve of PVP-I eye drops and PVP-I *in-situ* gel eye drops (n=3).**

As results shown in Fig 10, PVP-I *in-situ* gel eye drops had a significantly sustained-release character compared with conventional povidone iodine eye drops, and extended PVP-I release steadily for about 5 h.

**Povidone iodine *in-situ* gel eye drops ophthalmic retention study:**

Placed 1 ml normal PVP-I saline and PVP-I *in-situ* gel eye drops in brown EP tube, added 0.5% fluorescein sodium respectively. Chose a healthy New Zealand rabbit, and made its head fixed. Dropped 50 µL fluorescent labelled PVP-I normal saline solution into its left eye and made it close passively for 10s. Observed fluorescence condition of left eyes at 0, 2, 4, 6, 8 and 10 min via slit lamp; dropped 50 µL PVP-I *in-situ* gel eye drops into its right eye and made it close passively for 10 s. Observed fluorescence conditions of the right eyes at 0, 2, 5, 10, 20, 30, 40, 50 and 60min with a slit lamp.

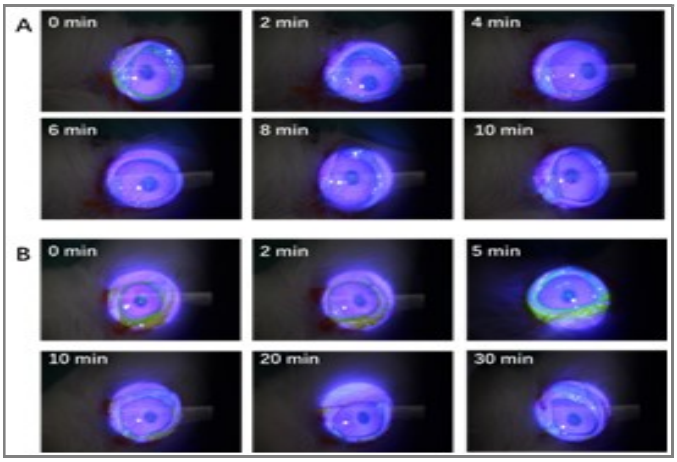


**Fig 11. The fluorescence photographs of the retention of PVP-I solution and PVP-I *in-situ* gel eye drops in rabbit eyes.**

## EVALUATION OF *IN SITU* GEL:

### Gelling capacity:

Gelling capacity of formulation is determined by placing a drop of the formulation in a vial containing 2.0 ml of freshly prepared simulated tear fluid and time taken for its gelling is noted [107].

### Tonicity:

Isotonicity is an important characteristic of ophthalmic formulation which has to be maintained to prevent any tissue damage or irritation to the eye. It refers to the osmotic pressure exerted by salts in aqueous solution. Ophthalmic formulation must possess osmotic pressure within the range of 290 to 310 m Osmol/kg. Tonicity is measured by using an Osmometer [109,110].

### Texture Analysis:

The consistency, firmness, and cohesiveness of *in situ* gel are assessed by using texture profile analyzer. This mainly indicates gel strength and easiness in administration. Texture analysis provides information on hardness, compressibility and adhesiveness which can be correlated with various parameters like ease of removal from container, good spreadability on corneal surface and adherence to mucous layer in order to prolong residence time [111].

### Transcorneal permeability Study:

Transcorneal permeability of drugs is evaluated by using goat eye cornea. The fresh whole eyeball of goat is obtained from a local butcher's shop and transported in a laboratory in normal saline solution (4 °C). Cornea is then carefully excised along with 2 to 4 mm of surrounding sclera tissue and wash with saline solution. Excise cornea is placed in between the donor and receptors compartment of Franz diffusion cell in such a way that the epithelial surface faces the donor compartment. The receptor compartment is filled with freshly prepared ATF. Whole assembly is placed on a thermostatically controlled magnetic stirrer, temperature (37±0.5 °C) as well as stirring rate (20 rpm) is maintained. 1ml prepared formulation is placed in the donor compartment. Samples (0.5 ml) are withdrawn at a predetermined time interval of 1 to 5 h and the same volume is replaced by ATF. Samples are analyzed on either UV spectrophotometer or HPLC [112].

### Ocular irritation study:

As there is a ban on Draize study in many countries ocular irritation study of *in situ* formulation can be performed by one of the following methods.

**Accelerated stability study:**

A stability study for *in situ* formulation is carried out as per ICH guidelines to determine the physical stability of the formulation under accelerated storage conditions. Formulation is subjected to elevated temperatures and humidity conditions of 25±1 °C/ 60 % RH, 30±1 °C/ 65 % RH and 40±2 °C/ 75±5 % RH. Samples are withdrawn at the end of 0, 30, 60 and 90 days and then evaluated for active drug content [113].

## CONCLUSION:

*In situ* gelling system is novel and technically superior to existing technologies. It solves various problems of conventional drug delivery systems including less retention time, poor bioavailability, systemic side effects and poor patient compliance. It is less expensive and less toxic than the agents currently used for ophthalmic preparation. PVP iodine turns the surface of the eye brown for a few minutes, a characteristic that can serve as an indicator that it has properly applied. *In situ* gel forming Povidone eye drops can be used in the treatment of a number of ocular diseases. Development of *in situ* gel-based delivery systems is one of the best solutions for the number of diseases. Use of advanced polymers undergoes in situ gelation with the change in stimuli. *In situ* gel-forming systems seem to be preferred because they can be administered in the form of drop and create significantly fewer problems with vision.

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