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IN-SITU OPHTHALMIC GELS FOR THE TREATMENT OF EYE DISEASES

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ABSTRACT

Topical administration of a drug in the conjunctival cul-de-sac is the treatment of choice for diseases of the anterior segment of eye. Development of ophthalmic drug delivery systems has always been challenging because of the drawbacks with this route, like non-productive absorption, drainage, induced lacrimation, tear turn over, impermeability of drugs to cornea. New approaches have been investigated for delivery of drugs to the eye by means of polymeric delivery of ophthalmic drugs to the pre-and intra ocular tissues, have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drug. Certain new approaches to increase the ocular bioavailability, duration of the drug action and to reduce the undesirable side effects are by using drug carriers that regulate pre-corneal drug loss and improve the corneal contact time. Many of these systems prolong ocular bioavailability but do not control drug penetration through the cornea. Consequently, the drug concentration at the site of action might remain inadequate. Therefore, it is necessary to develop safer, efficacious and more acceptable ocular therapeutic system. The ocular bioavailability of the drugs can be improved by prolonging their residence time in the cul-de-sac and by increasing their corneal permeability. There are various new dosage forms like *in-situ* gel, collagen shield, etc.

INTRODUCTION: Ophthalmic drug delivery is one of the challenging endeavors facing the pharmaceutical scientist today. The structural and functional aspects of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to overcome the protective barriers of the eye without causing permanent tissue damage [1].

The major problems in conventional liquid ophthalmic formulations are washing out of drug from the pre-corneal area immediately upon instillation because of constant lachrymal secretion, nasolacrimal drainage and short precorneal residence time of the solution. To increase precorneal residence time and ocular bioavailability, different ophthalmic delivery system such as viscous solutions, ointments, gels, suspensions or polymeric inserts are used. But because of blurred vision (e.g. ointments) or lack of patient compliance (e.g. inserts), these formulations have not been widely accepted. This problem can be overcome by using in situ gel forming ocular drug delivery system, prepared from polymer, exhibit sol-to-gel phase transition due to a change in a specific physio-chemical parameter (pH, temperature, ion-sensitive) [2].

In situ gels are conveniently dropped as a solution into the conjunctival sac, where they undergo a transition into a gel with its favorable residence time. The sol-gel transition occurs as a result of a chemical/physical change induced by physiological environment. This type of gel combines the advantage of a solution being patient convenient with the favorable residence time

of a gel for enhancing the ocular bioavailability [3].The principal advantage of in situ gels is that they can be easily administered with accurate and reproducible dose compared to that they can be easily instilled in liquid form, and are capable of prolonging the residence time [4].

Ideally, an *in-situ* gelling system should be a low viscous, free flowing liquid to allow for reproducible administration to the eye as drops, and the gel formed following phase transition should be strong enough to with stand the shear forces in the cul-de-sac and demonstrated long residence times in the eye. In order to increase the effectiveness of the drug, a dosage form should be chosen which increases the contact time of the drug in the eye. This may then prolong the residence time of the gel formed in situ along with its ability to release drug in sustained manner will assist in enhancing the bioavailability, reduce systemic absorption and reduce the need for frequent administration leading to improved patient compliance [5].

Gel formulations have found to be successful in achieving much better drug product effectiveness, reliability and safety. In this regard, poloxamer is very useful with majority of hydro gels, which undergo reversible volume and /or sol-gel phase transitions in response to physiological (temperature) stimuli [6].

Ocular drug delivery systems based on the concept of in-situ gel formation are aimed at longer precorneal residence time, improved ocular bioavailability and improved patient acceptability. Development of ophthalmic drug delivery systems has always been challenging.

The commonly used route for the drug delivery to the anterior segment of the eye has been the conjunctival cul-de-sac. Because of the drawbacks with this route, new approaches have been investigated for delivery of drugs to the eye by means of polymeric delivery systems. Ocular bioavailability from the conventional eye drops is poor and only a fraction of an administered dose (less than 1-3%) reaches the intra ocular tissues.

Thus there is a clear necessity of ocular bioavailability to be increased to at least 15-20%. The ocular and systemic side effects of ocular drugs are primarily related to overdosing and result from the absorption of ocular drugs through the naso mucosal lining. Ocular products need to be designed such that will be absorbed preferentially through the ocular tissues rather than through the ocular nasal mucosa in order to reduce, sometimes life threatening side effects. The ocular bioavailability of the drugs can be improved by prolonging their residence time in the cul-de-sac and by increasing their corneal permeability.

Two approaches have been attempted, namely maximizing the corneal drug absorption and minimizing the precorneal drug loss, and the use of devices which provide continuous delivery of ophthalmic drugs to the pre-and intra ocular tissues, to increase the bioavailability and the duration of therapeutic action of ocular drugs.

Challenges in developing an Ophthalmic Drug Delivery System:

1. **Anatomical and physiological features of the eye:** Many excellent reviews can be found in the literatures that describe the anatomical and physiological features of the eye, written from the perspective of drug delivery. Many of these anatomical and physiological features interfere with the fate of the administered drug. First and foremost are blinking, tear secretion, and nasolacrimal drainage. Lid closure upon reflex blinking protects the eye from external aggression. Tears permanently wash the surface of the eye and exert an anti-infectious activity by the lysozyme and immunoglobulin's they contain. Eventually the lachrymal fluid is drained down the nasolacrimal pathways, then pharynx and esophagus. This means that a portion of the drug is systematically delivered as if by the oral route. During administration, a part of an aqueous drop instilled in the patient's cul-de-sac is inevitably lost by overflow/drainage, since the conjunctival pouch can accommodate only approximately 20 µL of added fluid [7-9].

2. **Drug delivery to the internal regions of the eye:**

   a. **Eye Penetration of Drugs Administered Locally to the Eye:** If the drug is not intended to act on the external surface of the eye, then the active ingredient has to enter the eye. There is

consensus that the most important route is transcorneal; however, a non-corneal route has been proposed and may contribute significantly to ocular bioavailability of some ingredients, e.g., timolol and insulin.[10] In addition, the sclera has also been shown to have a high permeability for a series of blocking drugs. Precorneal tear film produced by tear secretion keeps the cornea moist, clear, and healthy and is spread by the motion of eyelids during blinking. Drugs acting on tear secretion, physicochemical status of the tear film, and blinking can modify transcorneal drug permeation [11].

b. **Eye penetration of systemically administered drugs:** There are blood-eye barriers. Aqueous humor is produced by the ciliary epithelium in the ciliary processes. It is frequently named an ultra filtrate, since the ciliary epithelium prevents the passage of large molecules, plasma proteins, and many antibiotics. Some molecules can be secreted in aqueous humor during its formation. Inflammation associated with injury, infection, or an ocular disease, e.g., uveitis, disrupts the blood–aqueous humor barrier and drugs enter the aqueous humor and reach the tissues of the anterior segment. There is a blood retina barrier and there is one between blood and vitreous humor complicated by the high viscosity of the latter, which prevents diffusion of the drugs in the posterior part of the eye. Delivery of drugs to the posterior pole and to the retina is extremely difficult.

3. **Assessment of performance of Ophthalmic Formulations**:

Pharmacokinetics:

1) **Rabbits***:* Assessment of the performance of a modified-drug-release dosage form relies upon changes in bioavailability. When dealing with systemically administered dosage forms, kinetic studies of plasma levels are the basic tool to establish bioavailability. Needless to say, plasma levels are irrelevant to assess ocular bioavailability of topically administered ophthalmic drugs. However, assessment of the performance of a modified-release ophthalmic drug delivery system is based upon pharmacokinetic and/or pharmacodynamic studies. There is a long history of invasive studies (e.g., aqueous humor levels) in animals, mainly in albino rabbits. This is because the rabbit is a very convenient animal in which to assess transcorneal penetration as a function of various factors such as salt, pH, adjuvants, etc. The rabbit and human eye do exhibit some similarities; the cornea is very similar in both species (but for the absence of Bowman's membrane in rabbits) and the aqueous humor composition is very similar in both species.

However, essentially, rabbits and humans were not created equal in terms of eye physiology. Rabbits blink only a few times per hour whereas humans blink 15–20 times per minute. Tear turnover is approximately 7% per minute in rabbits, compared to 16% in humans. The rabbit has a third eyelid - the nictitating membrane. This structure does not exist in humans. Also, the drainage rate constant is approximately 0.545/min in rabbits and three times larger, approximately 1.545/min in humans. In general, therefore, the respective precorneal parameters between rabbit and human are dissimilar. This means that formulation modified to change their behaviour in the front of the cornea can act differently in the two species.

It is possible to obtain aqueous humor samples from patients undergoing cataract surgery, where the anterior chamber is open. This practice is not carried out very frequently and has serious ethical implications. However, it provides a unique opportunity to compare aqueous humor levels obtained in humans versus those obtained in rabbits. It is interesting to note that data published for the drug dorzolamide tend to conclude that the transcorneal penetration is quite similar in the two species [12, 13].

2) **Humans***:* Clearly, human studies that assess the performance of a modified-release ophthalmic drug delivery system rely essentially on non invasive methods. Precorneal disposition can be studied using tear sampling and measurement of tear levels of the drug(s). It should be noted,

however, that such a procedure can induce excessive blinking and tear production in subjects sensitive to the sampling pipette, and therefore induce a bias in the results. Moreover, when dealing with formulations that do not mix rapidly with tear film, one can sample of tear levels of the drug(s). It should be noted, however, that such a procedure can induce excessive blinking and tear production in subjects sensitive to the sampling pipette, and therefore induce a bias in the results. Moreover, when dealing with formulations that do not mix rapidly with tear film, one can sample a small piece of the formulation itself, thus making the assay results from such a sample meaningless.

Pharmacodynamics: Drug pharmacodynamics is used when pharmacokinetic properties cannot be employed. Some biological responses, such as miosis, mydriasis, intraocular pressure, and bactericidal activity, are easy to assess quantitatively, whereas the appreciation of leakage from the retinal vessels is by far more difficult. It is mandatory when using pharmacological activity as a measurement of changes in bioavailability not to overlook the need to be in the linear part of the dose-response curve .Otherwise, even with a change in C_{max}, the response will plateau and nothing can be deduced from the experiment**.**

4. **Mechanism of controlled sustained drug release into the eye:**

   1) The corneal absorption represents the major mechanism of absorption for the most conventional ocular therapeutic entities.

   2) Passive Diffusion is the major mechanism of absorption for nor-erodible ocular insert with dispersed drug.

   3) Controlled release can further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solution. The existing ocular drug delivery systems are thus fair and inefficient. The design of ocular system is undergoing gradual transition from an empirical to rational basis; Interest in the broad areas of ocular drug delivery has increased in recent years due to an increased understanding of a number of ocular physiological process and pathological conditions. The focus of this review is the approaches made towards optimization of ocular delivery systems by

   - Improving ocular contact time
   - Enhancing corneal permeability
   - Enhancing site specificity

5. **Pharmacokinetics of Ocular Drug Absorption:** Considering the eye as two compartments, pre-corneal and aqueous humor, rate at which drug disappears from the pre-corneal compartment can be expressed mathematically as follows [14];

$$\frac{dC_T}{dt} = \frac{-q_T C_T - (K_p S_c / h_c)(C_T - C_{AH})}{V_D e^{-K_{nl} t} + V_0}$$

and the rate at which drug disappears in aqueous humor compartment can be expressed as:

$$\frac{dC_{AH}}{dt} = \frac{(K_p S_c)}{V_{AH} h_c}(C_T - C_{AH}) - K_{eAH} \frac{C_{AH}}{V_{AH}}$$

Where; C_T is the drug concentration in the tear fluid, K_p specific trans corneal permeability rate, S_c surface area of cornea, h_c thickness of cornea, C_{AH} drug concentration in aqueous humor, V_D drop size of the drug instilled, K_{nl} $(0.25 + 0.0113\ V_d)$ min^{-1}, V_0 normal resident tear volume, V_{AH} volume of aqueous humor, and V_D volume of drug pool in the pre-corneal area after instillation of the drug.

In-situ **Gelling Ocular Systems:** One traditional way to alleviate the problem of prolonging the contact time of the drug is by increasing the viscosity of the instilled solution by incorporating water-soluble polymers. Liquid dosage forms are highly acceptable from the patient community as eye drops. A delivery system consist of phase transition polymers that are instilled in a liquid form and shift to the gel phase once in the cul-de-sac of the eye 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 from few minutes to few hours, then improved local bioavailability, reduced dose concentrations and

dosing frequency and improved patient acceptability, may be achieved. The concept of in-situ gel formation should provide these properties.

Ocular drug delivery systems based on the concept of in-situ gel formation are aimed at longer precorneal residence time, improved ocular bioavailability and improved patient acceptability. From the point of tissue compatibility, sodium alginate with high glucuronic acid content and gellan gum, an anionic exocellular polysaccharide of microbial origin, possess excellent biocompatibility and have a characteristic property of cation induced gelation.

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The conventional liquid ophthalmic formulations (eye drops) show low bioavailability because of spillage by overflow, dilution of drug by tear turn over, naso-lachrymal drainage, systemic drug absorption and enzymatic metabolism [15].

An increase in the dosing frequency or the use of highly concentrated solutions to compensate for the short ocular residence time is undesirable because of poor patient compliance and the twin risks of local and systemic toxicity. To increase the ocular bioavailability and duration of drug action various ophthalmic vehicles such as viscous solutions, ointments/gels or polymeric inserts have been used.

The corneal contact time has been increased to varying degrees by these vehicles, but because of blurred vision (ointments), lack of patient compliance (inserts), sticking of lids (gels), they have not been widely accepted. Therefore other systems, which combine the ease of administration of liquid dosage forms with the prolonged residence time of insert, are being investigated actively, and few have been commercialized.

From the point of view of patient acceptability, a liquid dosage form that can sustain the drug release and remain in contact with the cornea for extended periods of time is ideal. If the pre-corneal residence time of a drug could be improved from 5 minutes to say, a few hours, then improved local bioavailability, reduced dose concentrations and dosing frequency and improved patient compliance may be achieved.

Drug delivery systems based on concept of *in situ* gel formation should provide these properties. These delivery systems are made from polymers that exhibit sol-gel phase transition due to physicochemical changes in their environment, in this case, the cul-de-sac of the eye.

A variety of polymers with different mechanisms of sol-gel phase transitions have been investigated to develop *in situ* gel forming systems. Among them are;

1. Poloxomer 407, tetronics and ethyl (hydroxy ethyl) cellulose- whose solution viscosity increases upon increasing the temperature to that of the eye [16].
2. Cellulose acetate phthalate (CAP) latex-coagulates when its native pH of 4.5 is raised by the tear fluid to 7.4 [17].
3. Carbopol solutions which are acidic and less viscous, transform to stiff gels upon increase in pH [18].
4. Alginates with high G content form three dimensional ionotropic hydrogel matrices, generally by the preferential interaction of Ca^{2+} ions of the tear fluid with the G moieties, resulting in the formation of homogenous gels [19].
5. Gelrite®, low acetyl gellan gum, like alginate, gels in the presence of Ca^{2+} ions in tears [20].

Paulsson *et al.* investigated the rheological properties of Gelrite in physiological conditions of eye. Na+ was found to be the most important gel-promoting ion *in vivo*. Gels were formed in tear fluid even at low concentrations of Gelrite i.e., at 0.1%. Samples with concentrations of Gelrite of 0.5-1% do not require more ions than 10-25 % of those in tear fluid to form gels. These finding explain the good performance of Gelrite *in vivo* [21].

Pluronic F-127 (Thermo sensitive polymer) and chitosan (pH Sensitive polymer and permeation enhancer) as a gelling vehicle have been used for the formulation of timolol maleate sustained *in situ* gel ocular delivery system. The developed formulation was clear, isotonic solution that converted to gel at temperatures above 35^{o}C and pH 6.9-7.0. A significant higher drug transport across corneal membrane and increased ocular retention time was observed using the developed formulation [22].

Pandit *et al.* have formulated and evaluated an ocular formulation of ciprofloxacin based on the concept of ion-activated *in situ* gelation using gellan gum (Gelrite®), a novel ophthalmic vehicle gels in the presence of mono or divalent cations, present in the lachrymal was used alone and in combinations with sodium alginate as a gelling agent. The developed formulations were therapeutically efficacious and provided sustained release of the drug over an 8 hour period *in vitro* [23].

Stewart *et al.* had evaluated and compared the efficacy and safety of timolol maleate (0.5%) gel forming solution containing gellan gum versus timolol maleate 0.5% in xanthan gum. The results demonstrated that, gel-forming solution lowers intraocular pressure 8 hours after dosing than does in xanthan gum, but safety appears similar between these products [24].

A methyl prednisolone ester of gellan (Gellan-MP) was synthesized. The various sustained release dosage forms evaluated were gellan-MP films, gellan films with physically incorporated MP suspended in 0.6% w/w gellan dispersion in water. The control dosage form was a suspension of MP in normal saline. MP concentrations in the tear fluid of New Zealand white rabbits were measured after ocular application of the dosage forms.

In vitro, gellan-MP films released covalently bound MP in an approximate zero order pattern, whereas the release of physically incorporated MP from the gellan eye drops and films followed a square root of time relationship and anomalous kinetics, respectively. Compared with the MP suspension control, gellan-MP films yielded an approximately 4 fold higher area under tear fluid concentration versus time curve, but exhibited a tendency to slip out of the eye due to a higher degree of swelling. The area under tear fluid concentration of the films was approximately equal to that of the control, while that from the eye drops showed 2.6 fold increases than the control and also provided ease of administration [25].

Hartmann *et al*. had reported the influence of artificial tear fluid (AT) and the rheological behavior of ionic and non-ionic ophthalmic polymer excipients. In usual concentrations, PVA, PVP, Dextran, HPMC, HEC and MC did not show any changes in their rheology. In contrast, solutions of PAA, Sodium hyaluronate (S-Hya), Sodium alginate (S-Alg) and Chitosan decrease the apparent viscosity in contact with AT, while gellan solution increases the viscosity and shows thixotropy. The adhesion of selected polymers (polysaccharides) on mucin was in the order S-hya> gellan> S-Alg > dextran. Miosis testing of gellan containing formulations in rabbits shows a possible reduction of drug concentration from 2% to 0.5% obtaining the same bioavailability [26].

Lin *et al*., has developed and characterize a series of carbopol- and pluronic based in-situ gelling vehicles for ophthalmic drug delivery. It was found that the optimum concentration of carbopol solution for the *in-situ* gel forming delivery systems was 3%w/w and that of the pluronic solution was 14% w/w, the mixture of carbopol (0.3%) and Pluronic (14%) solutions showed a significant enhancement of gel strength in physiological condition; this gel mixture was also found to be free flowing solution at pH 4.0 and 25^{o}C, the rheological behavior were not affected by the incorporation of pilocarpine hydrochloride.

Both *in vitro* and *in vivo* pharmacological studies indicated that the carbopol / pluronic solution had a better ability to retain drug than the carbopol or pluronic solutions alone [27].

A 0.6% Gelrite® vehicle has been compared to an equi-viscous solution of hydroxy ethyl cellulose (HEC) using timolol maleate as a drug probe. *In vitro* release rates of timolol from HEC and Gelrite® gel were similar. *In vivo*, the formation of gel prolonged the corneal residence time and increased the ocular bioavailability of timolol in the cornea, aqueous humor and iris + ciliary body of albino rabbits [28].

Wei *et al.* developed a thermosetting gel with a suitable phase transition temperature by combining pluronic analogs and also examined the influence of incorporating mucoadhesive polysaccharide, sodium hyaluronate (HA-Na), on the ocular retention of gel. Dynamic rheological method and single photon emission computing tomography technique were used to *ex vivo/in vivo* evaluation of the thermosetting gels, respectively.

Gamma scintigraphic data demonstrated that the clearance of the thermosetting gel labeled with 99m Tc-DTPA was significantly delayed with respect to the phosphate buffered solution, and at least a threefold increase of the corneal residence time was achieved. But no further improvement in the ocular retention was observed by the addition of HA-Na due to substantially decreased gel strength [29].

A complimentary *in vivo* study for determining pre-corneal contact times in humans and in rabbits was performed. The elastic modulii of the gels increased with increasing concentration of electrolytes, the elasticity of the gels was independent of Gelrite® concentration. The human contact times increased up to 20 hours with decreasing osmolality of the formulations [30].

A pH triggered *in situ* gelling vehicle for ophthalmic drug delivery using Carbopol 980 NF(gelling agent) in combination with HPMC (viscosity enhancer) was developed and the effect of Hydroxy propyl beta cyclodextrin (HP-β-CD)on the aqueous solubility and *in vitro* corneal permeation of puerarin were investigated by Wu *et al.* (2007). The solubility of the drug was increased proportionately with HP-β-CD and at 5% HP-β-CD, corneal permeability was significantly increased.

When carbopol and HPMC at concentrations 0.1% and 0.4 % w/v respectively, an *in situ* gel that had an appropriate gel strength and gelling capacity were obtained and showed pseudo plastic flow under physiological and non-physiological conditions. Both *in vitro* and *in vivo* pharmacokinetic studies indicated that the combined polymer performed better in retaining puerarin than eye drops did and proves the viable alternative to enhance the ocular bioavailability and patient compliance [31].

A Novel copolymer, poly (N-isopropylacrylamide)-chitosan (PNIPAAm-CS) was investigated by Cao *et al.*, 2007 for its thermo-sensitive *in situ* gel-forming properties and potential utilization for ocular drug delivery. The *in vivo* ocular pharmacokinetics of timolol maleate in polymer solution were evaluated and compared to that of conventional eye drops solution by using rabbits according to the micro dialysis method and the results were confirmed the potentially as a thermo sensitive polymer with good bioavailability and efficacy but little cytotoxicity was observed during MTT assay in the concentration range of 0.5 to 400 μg/ml[32].

Ma *et al.,* 2007, demonstrated Pluronic-g-PAA co-polymer as a promising *in situ* gelling vehicle for ophthalmic delivery as the rheology, *in vitro* and *in vivo* studies shows the good correlation in the improvement of pre-residence time, bio-adhesiveness, drug residence time and total drug residence amount in rabbit conjunctival sac when compared to conventional drops [33].

Poloxamer analogs and carbopol based *in situ* gelling and mucoadhesive ophthalmic delivery system for the delivery of puerarin was developed by Qi *et al.* The combined solutions converted to firm gels under physiological condition and attach to the ocular mucosal surface for a relative long time. The incorporation of carbopol 1342P NF did not affect the rheology but enhanced the mucoadhesive force significantly. The *in vitro* studies demonstrated diffusion- controlled release from the combined solutions over a period of 8 hours. *In vivo* evaluation indicated the combined solutions had better ability to retain drug than poloxomer or carbopol alone [34].

Gamma Scintigraphic studies were carried out to compare isoviscous Gelrite® solution (0.6%) and HEC solution (0.5%) with an isotonic saline solution in man. A significant retention of the Gelrite® formulation was found when compared to the HEC and saline solution, with the mean pre-corneal residence half life being 1089± 1485 seconds, 81±89 seconds and 22±19 seconds, respectively [35].

Liu *et al* described the formulation and evaluation of a sustained gel in which a hydroxy propyl beta cyclodextrin (HP-β-CD) as a penetration enhancer in combination with HPMC as a vehicle. They reported

that the developed formulation was efficacious, non-irritant, and provided sustained release of the drug over 8 h our period *in vitro* and 7 hour period *in vivo* [36].

Gunning *et al.* compared the ocular hypotensive activities of two potent topical carbonic anhydrase inhibitors, sezolamide (MK 417) and dorzolamide (MK 507), formulated in Gelrite® Vehicle. Duration of action of both the compounds was slightly prolonged by the use of Gelrite® vehicle, when compared to earlier studies [37].

A long acting ophthalmic formulation of carteolol containing alginic acid as a potential vehicle for prolonging the therapeutic effect was reported by Sechoy *et al*. The *in vitro* studies suggested the ionic interaction of alginic acid. The adhesive behavior of alginic acid was better than hydroxy ethyl cellulose. The intraocular pressure measurements of the rabbit eyes showed that alginic acid significantly extended the duration of pressure reducing effect of the drug to 8 hours. The overall results indicated that the alginic acid vehicle as an excellent drug carrier, well tolerated polymer for the sustained delivery of the drug to ocular tissues [38].

A study was reported by El-Kamel *et al.,* using the same drug (carteolol) and environmentally responsive gelling agent Gelrite®. As the concentration of gelling agent increases the drug release decreased. At 0.4 w/w concentration, Gellan showed improved bioavailability as compared with the commercial aqueous solution [39].

Hommer *et al.,* compared the ocular hypotensive effect of 0.25% timolol in Gelrite®, once daily (TG) to that of 0.25% timolol solution twice daily (TS). The results of this study supported the hypothesis of a comparable hypotensive effect of peak and trough of TG and TS. Furthermore, TG has an acceptable tolerability profile. The incidence of blurred vision and foreign body sensation was higher in TG [40].

Hartmann investigated the effect of artificial human tears containing calcium or magnesium ions on the rheological behavior of 0.6% gellan gum ophthalmic solutions, the release of pilocarpine hydrochloride *in vitro* and their miotic effect in rabbits. Pure 0.6% gellan gum showed pseudo plastic flow properties and nearly no thixotropy. The addition of artificial tears led to plastic flow properties and an increase in thixotropy, compared with an aqueous pilocarpine formulation. The release properties of the gellan gum formulations were significantly decreased on addition of artificial tears and more so on adding Ca^{2+} or Mg^{2+} ions to artificial tear fluid. A significantly prolongation of drug effect was not measurable *in vivo* when Ca^{2+} or Mg^{2+} were applied before instilling the gellan gum-pilocarpine formulation [41].

Rozier *et al.* developed a functionality test ensuring the consistency of the dosage form gelling property and a reproducible pharmacological effect. The rupture strength of the gel was shown to be a reliable indicator of the ocular drug bioavailability in albino rabbits. The test parameters susceptible to influence the test results were identified, evaluated and optimized. The influence of the raw material characteristics and the processing parameters on the final product gel strength were determined and optimized and the finished product specifications also established [42].

Gelrite® was tested in humans for its efficacy as an ophthalmic vehicle by a non-invasive fluorometric technique. Fluorescein was used as the tracer and its concentration in the anterior chamber was used as the principal measure of bioavailability. The gel afforded a two fold increase in the penetration of fluorescein compared with an isotonic buffer solution [43].

The formulation and evaluation of an ophthalmic drug delivery of an antibacterial agent, ofloxacin, based on the concept of pH triggered *in situ* gelation was investigated. Carbopol® 940 was used as the gelling agent in combination with HPMC (Methocel E50LV), which acted as a viscosity enhancing agent. The developed formulations were therapeutically efficacious, stable, non-irritant and provided sustained release of the drug over an 8-hour period [44].

In order to reduce the total polymer content and improve the gelling properties, Joshi *et al* first used the combination of polymers in the delivery system. The main idea is that aqueous composition of reversible gel in response to simultaneous variations in at least two physical parameters, such as pH, temperature and ionic strength can be formed by using a combination of polymers, which exhibit reversible gelation properties [45].

The rheological characterization of an *in situ* system prepared by a combination of carbopol and methyl cellulose (MC) was carried out at two different pH (4.0 and 7.4) and temperatures (25 and 37^{o}C). The studies indicated a pseudo plastic behavior and an increase in pH from 4.0 to 7.4 and temperature from 25 and 37^{o}C, resulted in an increase in viscosity, shear stress and yield point, and the magnitude of changes being highest when both the temperatures were altered simultaneously.

An increase in concentration of either carbopol or MC, or an increase in MC molecular weight resulted in an increase in shear stress, viscosity and yield point. Among the compositions studied, a solution containing 1.5% MC and 0.3 % carbopol was found to have low viscosity, and formed a strong gel under simulated physiological conditions [46].

The rheological properties of an aqueous solution containing Carbopol (974 NF) and HPMC, were evaluated as a function of temperature and pH and were found to be similar to those of pure Carbopol (974 NF) solution. In addition, the carbopol- HPMC gels decreased the *in vitro* release of incorporated timolol maleate [47].

Lin and Sung characterized a series of carbopol and pluronic- based solutions as *in situ* gelling vehicles for ophthalmic drug delivery. The rheological properties, *in vitro* release as well as *in vivo* pharmacological response of various polymer solutions, including carbopol, pluronic and carbopol/ pluronic solution, were evaluated. It was found that the optimum concentration of the carbopol solution for the *in situ* gel forming delivery systems was 0.3 % w/w and that for Pluronic solution was 14 % w/w.

The mixture of 0.3 % and 14 % pluronic showed a significant enhancement in gel strength in the physiological condition; this gel mixture was found to be free flowing at pH 4.0 and 25^{0}C. The rheological behavior of carbopol / pluronic solution was not affected by the incorporation of pilocarpine hydrochloride. Both the *in vitro* release and *in vivo* pharmacological studies indicated that the carbopol/ pluronic solution has better ability to retain drug than the carbopol or pluronic solutions alone [48].

Pluronic F127 (PF 127) based formulations of timolol maleate (TM) aimed to enhance its ocular bioavailability were developed (El-Kamel, 2002) and the effect of isotonicity agents and PF 127 concentrations on the rheological properties of the prepared formulations was examined. In an attempt to reduce the concentration of PF 127 without compromising the *in situ* gelling capabilities, various viscosity enhancing agents were added to PF 127 solution containing 0.5% TM.

The viscosity and the ability of PF 127 gels to deliver TM, *in vitro*, in absence and presence of various viscosity enhancing agents were also evaluated. At the used concentration, some of the examined isotonicity agents have effect on the viscosity of TM gel. However, the viscosity of gel increased as the PF 127 concentrations increased. The slowest drug release was obtained from 15 % PF 127 formulations containing 3% Methyl cellulose. *In vivo* studies showed that the ocular bioavailability of TM, measured in albino rabbits increased by 2.5 and 2.4 fold for 25% PF 127 gel formulation and 15 % PF 127 containing 3% methyl cellulose, respectively, compared with 0.5% TM aqueous solution[49].

Studies have been carried out on a number of pluronic polyols with the aim of determining factors which influence the transition temperature of the hydrogels. The sol-gel transition temperatures, Tm, were measured for aqueous solutions of the polyols with and without additives such as sodium chloride, potassium chloride, urea, ethanol, sodium sulfate, and sodium dodecyl sulfate. A linear relationship was found between the logarithm of the pluronic polyol concentration and the reciprocal of the gel-sol transition temperature for all polymers, such a relationship does seem to exist among the polymers having the same ratio of poly(oxypropylene) to poly(oxyethylene) units per mole of polymer (P/E ratio). All the pluronic polyols studied showed endothermic enthalpy change for the sol-gel process. These results were substantiated with data from calorimetric studies [50].

The distribution of a model 16-mer oligothymidtlate (pdT16) in several ocular tissues (cornea, conjunctiva, sclera, iris, lens, aqueous and vitreous humors was determined after instillation in the eye of various

dosage forms in a rabbit model. Radio labelled pdT16 was applied as a simple solution, a 27% poloxamer 407 gel, a suspension of liposomes or liposomes dispersed within a 27% poloxomer 407 gel. pdT16 concentrations were measured in the tissues and fluids by radioactivity counting at the intervals of 10 minutes, 2 hours and 24 hours. When the pdT16 solution was used, the highest concentrations were observed in the conjunctiva and the cornea, while a substantial amount of drug was also present in the sclera. Low concentrations were measured in the iris.

Using the same treatment protocol, the two liposomal formulations delivered low amounts of pdT16 to all ocular tissues, and particularly to the conjunctiva and the cornea. The poloxamer gel provided higher tissue concentrations of pdT16 than liposomes but lower than those observed with the solution except 10 minutes after administration in the iris where the amounts of pdT16 were higher when administered under the gel form [51].

Rheological measurements were performed to study the gel and sol-gel transition of an *in situ* gel, Poloxomer 407. The rheological measurements and a small *in vivo* study of ocular residence times in humans were used to evaluate poloxomer as an ocular vehicle. An increasing concentration of poloxomer resulted in a slightly increasing elasticity of the gels and a decreasing sol-gel transition temperature. The contact time increased with increasing concentration of poloxomer, which could be explained and correlated, with the rheology of poloxomer solutions/gels mixed with simulated tear fluid. The maximum contact time for the preparations studied was about 1 hour [52].

Gurny *et al.* used the gamma scintigraphy technique to monitor the ocular residence time of an ophthalmic preparation based on cellulose acetate phthalate (30% w/w, viscosity 50 mPas). The gelled system constituted an *in situ* micro reservoir of high viscosity. The pre-corneal residence time (half life) in rabbits was 400 seconds when compared to 40 seconds for a solution.

Pilocarpine formulated with cellulose acetate phthalate (CAP) maintained a constant miosis in the rabbit for up to 10 hours when compared to 4 hours with eye drops. This system is however, characterized by a high polymer concentration (30% w/w CAP) and low pH of the instilled solution may be a discomfort for the patient [53].

Ruel *et al.* investigated the physical properties of a chitosan-glycerophosphate (GP) thermo sensitive solution that gels at 37^0C and evaluated the *in vitro* release profiles of different model compounds. The gelation rate was dependent on the temperature and on the chitosan deacetylation degree. The solution containing 84% deacetylated chitosan could be stored for 3 months at 4^oC without apparent change in viscosity. The *in vitro* release profiles of the model compounds were dependent on the presence of GP in the chitosan solution, on their molecular weight and on the presence of lysozyme in the release media [54].

A thermo gelling drug delivery system composed of cellulose ether [ethyl (hydroxy ethyl) cellulose –EHEC, an ionic surfactant and water was characterized in the presence of timolol maleate with respect to phase and rheological behavior, as well as *in vitro* drug release. The phase studies revealed that gelling systems may be formed with 0.34% w/w timolol maleate, and that the gelling behavior was sensitive to the surfactant concentration and ionic strength of the solution. The release of timolol maleate fro the gels was retarded compared to a non-gelling EHEC system [55].

Sultana *et al.,* demonstrated the carbopol/methyl cellulose mixture can be used as an *in situ* gelling vehicle to enhance the ocular bioavailability of pefloxacin mesylate. The rheological, *in vitro* and *in vivo* response of combined polymer solutions was evaluated. It was found that the optimum concentration of carbopol solution for the *in situ* gel forming delivery system was 0.3% and 1.5 % for methyl cellulose.

The mixture of carbopol and methyl cellulose at above concentrations showed a significant enhancement in gel strength in the physiological condition; this gel mixture was free flowing at pH 4.0 and 25^0C. The dug levels in the aqueous humor of the rabbits were well above the MIC values of relevant bacteria after 12 hours.

All studies showed that carbopol/methyl cellulose solution had better ability to retain drug than did the carbopol or methyl cellulose alone [56].

Sultana *et al.* developed an ion activated *in situ* gelling Gelrite® based formulation containing fluoroquinolone pefloxacin mesylate and compared with marketed drops in efficacy for the treatment of artificially induced bacterial conjunctivitis in rabbits. The formulations were evaluated for their rheology, *in vitro* release, antimicrobial efficacy and efficacy against bacterial conjunctivitis. The formulations exhibit first order release rate for 12 hrs and effective against selected microorganisms and therapeutically effective against marketed eye drops [57].

The orally administered acetazolamide has a limited use in glaucoma due to the systemic side effects associated with its use. It has been reported to show little effect on the intraocular pressure (IOP) of human and rabbit eyes upon topical application, probably owing to its poor availability and instability at pH > 5.0. In order to enhance the bioavailability of the drug, contact time between the drug molecules and the ocular surface was increased using high viscosity water soluble polymers (PVA and HPMC) and by incorporating acetazolamide in an *in situ* forming ophthalmic drug delivery system.

Moreover, a penetration enhancer (EDTA) was also used in these formulations to increase the extent of absorption of the drug. Acetazolamide at a concentration of 10% was used and the formulations (eye drop suspensions) were evaluated for their *in vitro* pattern. The effect of these formulations on the IOP in normosensitive conscious rabbits was also investigated. These formulations were found to be therapeutically effective with a peak effect at 2 hours. A fall in IOP of up to 46.4% was observed with repeated administration of one of the formulation containing PVA, EDTA and Tween 80 [58].

Liu *et al.* studied alginate/ HPMC based *in situ* gelling ophthalmic delivery system for gatifloxacin based on the concept of ion-activated *in situ* gelation. The rheological behaviors, *in vitro* release and *in vivo* pre-corneal retention studies indicated that the alginate / HPMC solution retained the drug better than alginate or HPMC alone [59].

A series of alginate and pluronic based solutions as *in situ* gelling vehicles for ophthalmic delivery of pilocarpine were evaluated by Lin *et al*. The rheology, *in vitro* release and pharmacological response of these systems were evaluated. The pluronic solutions alone and mixture of alginate / pluronic solutions showed a significant increase in gel strength in the physiological condition [60].

Thermo-reversible gels formed *in situ* by aqueous solutions of an enzyme-degraded xyloglucan polysaccharide were evaluated as sustained release vehicles for the ocular delivery of pilocarpine hydrochloride. *In vitro* release of pilocarpine from gels formed by warming xyloglucan sols (1.0, 1.5 and 2.0 % w/w) to 34^{o}C followed root time kinetics over a period of 6 hours. The mitotic responses in rabbit following administration of xyloglucan sols were compared with those from *in situ* gelling Pluronic F127 sols and from an aqueous buffer solution containing the same drug concentration. Sustained release of pilocarpine was observed with all gels, the duration of mitotic response increasing with increase of xyloglucan concentration [61].

Cohen *et al.,* demonstrated that an aqueous solution of sodium alginate can gel in the eye without the addition of external calcium ions or other bivalent / polyvalent cations. The extent of alginate gelation and consequently the release of pilocarpine, depended on the % G residues in the polymer backbone. Alginates with G contents of more than 65%, such as Manugel, DMB, instantaneously formed gels upon their addition to simulated lachrymal fluid, while those having low G contents, such as Kelton LV, formed weak gels at a relatively slow rate.

In vitro studies indicated that pilocarpine was released slowly from the alginate gels, over a period of 24 hrs and the release occurred mostly via diffusion from the gels. IOP measurements of rabbit eyes treated with 2% (w/v) pilocarpine nitrate, in solution or in the *in situ* gel forming formulations composed of high G content alginate, indicated that a significantly extended the duration of the pressure reducing effect of pilocarpine to 10 hours as compared to 3 hours when pilocarpine nitrate was delivered as solution [62].

Gratieri et al. investigated the potential of a chitosan solution as well as an in situ gel-forming system comprised of poloxamer/chitosan as vehicles for enhanced corneal permeation and sustained release of fluconazole (FLU). The in vitro release studies showed

the sustained release of FLU from the poloxamer/ chitosan formulation. *Ex vivo* permeation studies across porcine cornea demonstrated that the formulations studied have a permeation-enhancing effect that is independent of chitosan concentration in the range from 0.5 to 1.5% w/w.

The chitosan solutions alone showed the greatest ex vivo drug permeation; however, the poloxamer/ chitosan formulation presented similar *in-vivo* performance than the chitosan solution at 1.0%; both formulations showed sustained release and about 3.5-fold greater total amount of FLU permeated when compared to simple aqueous solutions of the drug [63].

Rupenthal *et al*., compared ion-activated *in situ* gelling systems for ocular drug delivery and showed that all tested polymer systems were non-irritant. Precorneal retention studies revealed a biphasic rapid release for the solution with less than 40% radioactivity left on the ocular surface after 15 min, while formulations based on gellan gum, xanthan gum and carrageenan seemed to drain at an almost constant rate with more than 80% radioactivity remaining. This was in agreement with the *in-vivo* miotic studies, which demonstrated that the area under the curve and the miotic response at 120 min after administration for gellan gum, xanthan gum and carrageenan formulations of pilocarpine were increased by 2.5-fold compared to an aqueous solution, which demonstrates their potential use in ophthalmic formulations [64].

Wu *et al.,* investigated the correlation between the stability of baicalin and in situ pH-triggered gelling system. Carbopol (®) 974P (0.3%, w/v) was used as the gelling agent combined with hydroxypropylmethyl cellulose E4M (0.6%, w/v) which acted as a viscosity enhancing agent. *In-vitro* and *in-vivo* evaluations were performed using several techniques, namely confocal scanning light microscopy analysis, rheometry, Gamma scintigraphic technique and micro dialysis method.

The rheological behavior showed a significant enhancement in gel strength under physiological conditions, and the formulation provided sustained release of the drug over an 8-h period. In elimination studies, the radioactivity of formulation was always higher than that of the control solution.

Additionally, the AUC and C_{max} values were 6.1-fold and 3.6-fold higher than those of the control solution, respectively. The results demonstrated that an *in-situ* pH-triggered gelling system have better ability to keep baicalin stable and retain drug release than marketed baicalin eye drops to enhance the ocular bio-availability [65].

Shastri *et al.,* studied the formulation development of ophthalmic *in-situ* gelling system using thermo-reversible gelling polymer, i.e. Pluronic F 127 (PF127). Because of high concentration (20 to 25%w/v) of this polymer required for *in-situ* gelation causes irritation to the eye. So, to reduce this concentration, an attempt was made to combine the PF127 with other polymers like hydroxy propyl methyl cellulose (HPMC) as a viscosity increasing agent or with polymers like carbopol 940, xanthan gum, and sodium alginate (high glucuronic acid content) showing a pH and cation-triggered sol-gel transition, respectively.

Different batches were prepared of varying concentrations of these polymers with PF127 using cromolyn sodium 2%w/v in phosphate buffer pH 5.0. The formulations were optimized by the viscosity measurement and *in vitro* gelation study. Selected formulations were evaluated for *in vitro* drug release profile and indicated sustain drug release over a period of 10 h. Effect of sterilization on drug content, pH, clarity, and viscosity were also evaluated. Finally, we concluded that by using this type of combination system, we could reduce not only the concentration of individual polymers but also the side effects without compromising the in vitro gelling capacity as well as overall rheology of the system [66].

Qian *et al*., studied the thermo sensitive *in-situ* gelling vehicle using Poloxamer. The optimum concentrations of poloxamer analogs for the in situ gel-forming delivery system were 21% (w/w) poloxamer 407 and 10% (w/w) poloxamer P188. This formulation was able to flow freely under non physiological conditions and underwent sol-gel transition in the *cul-de-sac* upon placement into the eye. *In-vitro* release studies demonstrated a diffusion-controlled release from the poloxamer solutions over a period of 10 hours. *In-vivo* valuation indicated that the poloxamer solutions had a better ability to retain drug than eye drops [67].

Shastri *et al*., studied an in situ gelling thermo reversible mucoadhesive gel was formulated of an antibacterial agent, Moxifloxacin HCl using a combination of poloxamer 407 and poloxamer 188 with different mucoadhesive polymers such as Xanthan gum and Sodium alginate with a view to increase gel strength and bioadhesion force and thereby increased precorneal contact time and bioavailability of the drug. Formulations were found transparent, uniform in consistency and had good spreadability within a pH range of 6.8 to 7.4.

A satisfactory bioadhesion (3298 to 4130 Dyne/cm2) on the sheep's corneal surface and good gel strength (95 to 128 sec) was also observed. As the concentration of mucoadhesive polymers in the gel formulation increased, the rate of drug release decreased. The order of drug release was in order: Xanthan gum > Sodium alginate. It was concluded that a thermo reversible in situ gel of Moxifloxacin HCl can be formulated by combining with mucoadhesive polymers and used effectively as safe and sustained ocular drug delivery.

This combination provided greater bioadhesion force and gel strength as compared to the thermo reversible polymers i.e., poloxamer 407 (PF 127) or 188 (PF 68) when used alone [68].

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