



IN-SITU GELLING OPHTHALMIC DRUG DELIVERY SYSTEM: AN OVERVIEW

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ABSTRACT

Eye is the most vital organ of body. The usual ophthalmic dosage forms are account for 90% of currently accessible ophthalmic formulations. The major trouble encountered is quick precorneal drug loss. To improve ophthalmic drug bioavailability, there are considerable efforts directed towards newer drug delivery systems for ophthalmic administration. Newer research in ophthalmic drug delivery systems is directed towards an amalgamation of several drug delivery technologies, that includes to build up systems which is not only extend the contact time of the vehicle at the ocular surface, but which at the same time slow down the removal of the drug. There are various new dosage forms like *in-situ* gel, collagen shield, minidisc, ocular film, ocusert, nanosuspension, nanoparticulate system, liposomes, niosomes, dendrimers, ocular iontophoresis etc. Conventional delivery systems often result in poor bioavailability and therapeutic response because high tear fluids turn over and dynamics cause rapid elimination of the drug from the eyes. So, to overcome bioavailability problems, ophthalmic *in situ* gels were developed.

Keywords: *In-situ* gel, Novel ocular drug delivery system, pH-triggered *in-situ* system, Ion-activated *in-situ* system, Temperature evident *in-situ* system, Sol to gel.

INTRODUCTION

The main aim of pharmacotherapeutics is the attainment of an effective drug concentration at the intended site of action for a sufficient period of time to elicit the response. A major problem being faced in ocular therapeutics is the attainment of an optimal concentration at the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, non-productive absorption, transient residence time, and impermeability of corneal epithelium¹.

Various problems encountered in poor bioavailability of the eye installed drugs are²:

- Binding by the lachrymal proteins.
- Drainage of the instilled solutions;
- Lachrimation and tear turnover;
- Limited corneal area and poor corneal
- Metabolism;
- Non-productive absorption/adsorption;
- Tear evaporation and permeability;

The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug may be overcome by the use of a gel system that are instilled as drops into the eye and undergo a sol-gel transition in the *cul-de-sac*³.

For the therapeutic treatment of most ocular problems, topical administration clearly seems the preferred route, because for systemically administered drugs, only a very small fraction of their total dose will reach the eye from the general circulatory system. Even for this fraction, distribution to the inside of the eye is further hindered by the blood-retinal barrier (BRB).

At first sight, the eye seems an ideal, easily accessible target organ for topical treatment. However, the eye is, in fact, well protected against absorption of foreign materials, first by the eyelids and tear-flow and then by the cornea, which forms the physical-biological barrier. When any foreign material or medication is introduced on the surface of the eye, the tear-flow immediately increases and washes it away in a relatively short time. Under normal conditions, the eye can accommodate only a very small volume without overflowing. Commercial eye drops have a volume of ~30 μ L, which is about the volume of the conjunctival sac in humans; however, after a single blink, only an estimated 10 μ L remains⁴.

Consequently, there is a window of only ~5 to 7 minutes for any topically introduced drug to be absorbed and in many cases, no

more than 2% of the medication introduced to the eye will actually be absorbed.

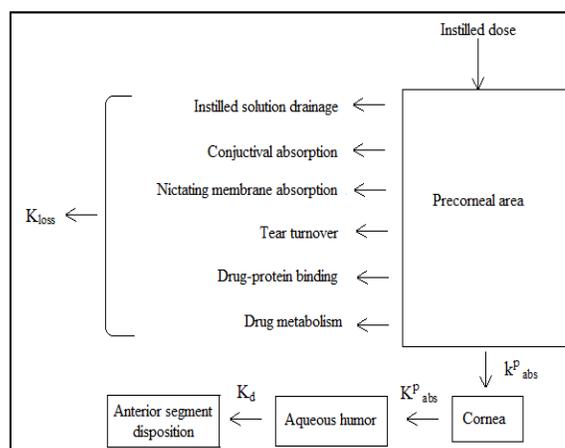


Fig. 1: Model depicting pre-corneal and ocular drug movement from topical instilled dose

The rest will be washed away and absorbed through the nasolacrimal duct and the mucosal membranes of the nasal, oropharyngeal, and gastrointestinal tract. For the remaining portion, the main biological barrier to penetration is represented by the cornea, which is very effective. The human cornea is composed of five tissue types with three of them, the epithelium, the endothelium, and the inner stroma, being the main barriers to absorption⁵.

VARIOUS APPROACHES OF IN-SITU GELATION

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 withstand 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 prolonged residence time of the gel formed *in situ* along with its ability to release drugs in sustained manner will assist in enhancing the bioavailability, reduce systemic absorption and reduce the need for frequent administration leading to improved patient compliance⁶.

Depending upon the method employed to cause sol to gel phase transition on the ocular surface, the following types of systems are recognized:

- pH-triggered systems: cellulose acetate phthalate (CAP) latex, carbopol, polymethacrylic acid (PMMA), polyethylene glycol (PEG), pseudolatexes.
- Temperature dependent systems: chitosan, pluronics, tetratics, xyloglucans, hydroxypropylmethyl cellulose or hypromellose (HPMC).
- Ion-activated systems (osmotically induced gelation): gelrite, gellan, hyaluronic acid, alginates.
- UV induced gelation
- Solvent exchange induced gelation.

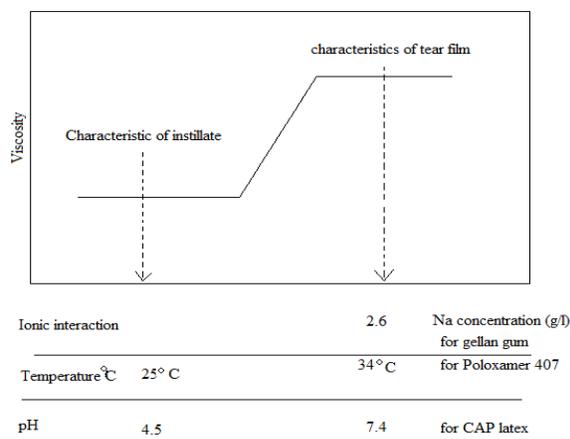


Fig. 2: Schematic representation of the viscosity change on the ocular surface when using ophthalmic *in-situ* gelling systems.

These (liquid) vehicles undergo a viscosity increase upon instillation in the eye, thus favouring precorneal retention. Such a change in viscosity can be triggered mainly by a change in temperature, pH or electrolyte composition.

pH-triggered *in-situ* gelation: Polyacrylic acid (Carbopol 940) is used as the gelling agent in combination with hydroxypropylmethylcellulose (Methocel E50LV) which acted as a viscosity enhancing agent. The formulation with pH-triggered *in-situ* gel is therapeutically efficacious, stable, non-irritant and provided sustained release of the drug for longer period of time than conventional eye drops. Another example cellulose acetate phthalate (CAP) is a polymer undergoing coagulation when the original pH of the solution (4.5) is raised to 7.4 by the tear fluid⁷⁻⁹.

Temperature triggered *in-situ* gel: The system is designed to use Poloxamer as a vehicle for ophthalmic drug delivery using *in-situ* gel formation property. The gelation temperature of graft copolymers can be determined by measuring the temperature at which immobility of the meniscus in each solution was first noted. The bioadhesive and thermally gelling of these graft copolymers expected to be an excellent drug carrier for the prolonged delivery to surface of the eye. Other example Poloxamer-407 (a polyoxyethylenepolyoxypropylene block copolymer, Pluronic F-127®) is a polymer with a solution viscosity that increases when its temperature is raised to the eye temperature¹⁰⁻¹¹.

Ion-activated *in-situ* gelation: Alginate (Kelton) is used as the gelling agent in combination with HPMC (Methocel E50Lv) which acted as a viscosity-enhancing agent. Gelrite gellan gum, a novel ophthalmic vehicle that gels in the presence of mono or divalent cations, present in the lachrymal fluid can be used alone and in combinations with sodium alginate as the gelling agent¹²⁻¹³.

Worked reviewed in the field of *in-situ* gel:

Over the last decades, an impressive number of novel temperature, pH, and ion induced *in-situ* forming solutions have been described in the literature. Each system has its own advantages and drawbacks.

The choice of a particular hydrogel depends on its intrinsic properties and envisaged therapeutic use.

Harish, N.M., et al., (2009), developed *in situ* gel of clotrimazole for oral candidiasis using pH-triggered system containing carbopol 934P (0.2-1.4% w/v) and ion-triggered system using gellan gum (0.1-0.75% w/v) along with HPMC E50 LV. Formulations were evaluated for gelling capacity, viscosity, gel strength, bio-adhesive forces, spreadability, microbiological studies and *in vitro* release. The optimized formulation was able to release the drug up to 6 h. The formulation containing gellan gum showed better sustained release compared to carbopol based gels¹⁴.

Ega Chandra Mohan, et al., (2009), formulated and evaluated *in-situ* gels for ciprofloxacin based on the concepts of pH-triggered *in-situ* gelation, thermo reversible gelation and Ion activated system. Poly acrylic acid (Carbopol 940) was used as the gelling agent in combination of hydroxypropyl methylcellulose, which acted as a viscosity-enhancing agent. (pH-triggered system). Pluronic F-127 (14%) was used as the thermal reversible gelation in combination of HPMC (1.5%) incorporation of HPMC was to reduce the concentration of pluronic required for *in-situ* gelling property, with 25% w/w pluronic F-127 reported to form good gels. Gellan gum (Gelrite) is an anionic exocellular polysaccharide by the bacterium *Pseudomonas elodea*, having the characteristic property cation-induced gelation (0.6%). The developed formulation was therapeutically efficacious, stable, non irritant and provided sustained release of the drug over six hours period, but Gelrite formulation showing long duration of release followed by combination of carbopol, HPMC and pluronic F-127 and HPMC. The developed system is thus a viable alternative to conventional eye drops¹⁵.

Wen-Di Ma, et al., (2008), prolonged the precorneal resident time and improves ocular bioavailability of the drug; Pluronic F127-*g*-poly (acrylic acid) copolymers were studied as *in-situ* gelling vehicle for ophthalmic drug delivery system. The rheological properties and *in vitro* drug release of Pluronic-*g*-PAA copolymer gels were investigated. The rheogram and *in vitro* drug release studies indicated that the drug release rates decreased as acrylic acid/Pluronic molar ratio and copolymer solution concentration increased. But the drug concentration had no obvious effect on drug release. The release rates of the drug from such copolymer gels were mainly dependent on the gel dissolution. *In vivo* resident experiments showed the drug resident time and the total resident amount in rabbit's conjunctival sac increased by 5.0 and 2.6 folds for *in-situ* gel, compared with eye drops. The decreased loss angle at body temperature and prolonged precorneal resident time also indicated that the copolymer gels had bioadhesive properties. These *in vivo* experimental results, along with the rheological properties and *in vitro* drug release studies, demonstrated that *in-situ* gels containing Pluronic-*g*-PAA copolymer may significantly prolong the drug resident time and thus improve bioavailability. Pluronic-*g*-PAA copolymer can be a promising *in-situ* gelling vehicle for ophthalmic drug delivery system¹⁶.

Himanshu Gupta, Sanyog Jain, et al., (2007), prepared and evaluated sustained ocular drug delivery from a temperature and pH triggered novel *in-situ* gel system using Pluronic F-127 (a thermosensitive polymer) in combination with chitosan (pH-sensitive polymer also acts as permeation enhancer) was used as gelling agent with timolol maleate¹⁷.

Cao, Y., et al., (2007), investigated a novel copolymer, poly (N-isopropylacrylamide)-chitosan (PNIPAAm-CS), for its thermosensitive *in-situ* gel-forming properties and potential utilization for ocular drug delivery. The thermal sensitivity and low critical solution temperature (LCST) were determined by the cloud point method. PNIPAAm-CS had a LCST of 32°C, which is close to the surface temperature of the eye. The *in vivo* ocular pharmacokinetics of timolol maleate in PNIPAAm-CS solution were evaluated and compared to that in conventional eye drop solution by using rabbits according to the microdialysis method. The results suggest that PNIPAAm-CS is a potential thermosensitive *in-situ* gel-forming material for ocular drug delivery, and it may improve the bio-availability, efficacy, and compliance of some eye drugs¹⁸.

El-Kamel, et al., (2006), formulated environmentally responsive ocular gel of carteolol HCl using gelrite as polymer. After *in vitro* release studies they concluded that gelrite formulation (0.4%w/w) containing 1% drug showed significantly improved bioavailability as compared to commercial aqueous solution¹⁹.

D. I. Ha, et al., (2006), prepared thermo-responsive and injectable hydrogels based on hyaluronic acid and poly (*n*-isopropylacrylamide) and their drug release behaviours²⁰.

Sultana, et al., (2006), developed ophthalmic delivery system for pefloxacin mesylate based on *in-situ* gel of gelrite and evaluated for rheological characterizations, antimicrobial efficacy, *in vitro* release pattern. The developed formulation showed better therapeutic efficacy than marketed preparation⁸.

Sreenivas, S.A., et al., (2006), designed, formulated and evaluated ofloxacin ocular inserts. Hydroxy propyl methyl cellulose, methyl cellulose, poly vinyl pyrrolidone and poly vinyl alcohol were used as polymers. PEG-400 was incorporated as plasticizer. The main purpose was to deliver the drug in zero order kinetics. Solvent casting technique was followed to prepare ofloxacin ocular films. Eight formulations were formulated and subjected to various physicochemical evaluations. Ocular inserts prepared were smooth and passed all the evaluation tests performed. Formulation OF2 shows a maximum cumulative percentage drug release of 91.27% at the end of 24 hours. Ocular inserts formulated also passed the test for sterility. They showed zero-order release of the drug in the *in vitro* and *in vivo* release studies. The drug in the films was found to be active against selected microorganisms as was proved by microbial efficacy studies. A high correlation coefficient was found between *in vitro* and *in vivo* release rate studies. Shelf-life of the product was found to be more than one year. The results of *in vitro*, *in vivo*, kinetic treatment (Zero order and Korsmeyer's regression values) and rate constant 'k' value suggest that OF2 was the best formulation among the formulations studied for formulating ofloxacin ocular insert²¹.

Liu Z., et al., (2006), describes the formulation and evaluation of an ophthalmic delivery system of an antibacterial agent, gatifloxacin, based on the concept of ion-activated *in situ* gelation. Alginate (Kelton) was used as the gelling agent in combination with HPMC (Methocel E50Lv) which acted as a viscosity-enhancing agent. The rheological behaviors of all formulations were not affected by the incorporation of gatifloxacin. Both *in vitro* release studies and *in vivo* pre-corneal retention studies indicated that the alginate/HPMC solution retained the drug better than the alginate or HPMC E50Lv solutions alone. These results demonstrate that the alginate/HPMC mixture can be used as an *in-situ* gelling vehicle to enhance ocular bioavailability and patient compliance²².

Liu Z., et al., (2005), describes the formulation and evaluation of an ophthalmic delivery system containing an antibacterial agent, enoxacin, based on the concept of ophthalmic sustained gel, in which 2-hydroxypropyl-beta-cyclo-dextrin (HP-β-CD) was used as a penetration enhancer in combination with hydroxypropyl-methylcellulose (Methocel F4M) which acted as a vehicle. The developed formulation was therapeutically efficacious, nonirritant, and provided sustained release of the drug over 8 h period *in vitro* and 7 h period *in vivo*. The developed system is a viable alternative to conventional eye drops²³.

Aminabhavi, T., M., et al., (2004), studied rheological properties, blend compatibility, and gel-forming capacity of carbopol-940, sodium alginate and gaur gum. These matrices were used in delivery of timolol maleate for ophthalmic applications. The viscosity of *in-situ* gel forming polymeric solutions was found to increase upon exposure to specific pH, ions and temperature of the eye ball. After *ex vivo* release studies on timolol maleate they concluded then the release could be extended when the drug is incorporated into hydrogel forming solutions²⁴.

Balasubramaniam, J., et al., (2003), describes the formulation and evaluation of an ophthalmic delivery system of an antibacterial agent, CPH, based on the concept of ion-activated *in-situ* gelation. gelrite, gellan gum, a novel ophthalmic vehicle that gels in the presence of mono or divalent cations, present in the lachrymal fluid

was used alone and in combinations with sodium alginate as the gelling agent. The developed formulations were therapeutically efficacious and provided sustained release of the drug over an 8-hr period *in vitro*¹².

Balasubramaniam, J., et al., (2003), *In vitro* and *in vivo* evaluation of the Gelrite gellan gum-based ocular delivery system for indomethacin develop an ophthalmic delivery system of the NSAID indomethacin, based on the concept of ion activated *in-situ* gelation. Gelrite gellan gum, a novel ophthalmic vehicle, which gels in the presence of mono or divalent cations present in the lacrimal fluid, was used as the gelling agent. The developed formulations were therapeutically efficacious (in a uveitis induced rabbit eye model) and provided sustained release of the drug over an 8-hour period *in vitro*²⁵.

Ishibashi, T., et al., (2003), investigated the retention of reversibly thermo-gelling timolol on human ocular surface using video meniscometry. The study showed that the reversibly thermo-gelling timolol was better retained at the ocular surface than conventional, aqueous timolol²⁶.

El-Kamel, A.H., et al., (2002), developed Pluronic F127 (PF127) based formulations of timolol maleate (TM) aimed at enhancing its ocular bioavailability. The effect of isotonicity agents and PF127 concentrations on the rheological properties of the prepared formulations was examined. In an attempt to reduce the concentration of PF127 without compromising the *in situ* gelling capabilities, various viscosity enhancing agents were added to PF127 solution containing 0.5% TM. The viscosity and the ability of PF127 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 had effect on the viscosity of TM gel. However, the viscosity of gel increased as the PF127 concentrations increased. The viscosity of formulations containing thickening agents was in the order of PF-MC 3%>PF-HPMC 2%>PF-CMC 2.5%>PF127 15%. The slowest drug release was obtained from 15% PF127 formulations containing 3% methylcellulose. *In vivo* study showed that the ocular bioavailability of TM, measured in albino rabbits, increased by 2.5 and 2.4 fold for 25% PF127 gel formulation and 15% PF127 containing 3% methylcellulose, respectively, compared with 0.5% TM aqueous solution¹¹.

Kaur, I.P., et al., (2002), studies the (1) the barriers that decrease the bioavailability of an ophthalmic drug; (2) the objectives to be considered in producing optimal formulations; and (3) the approaches being used to improve the corneal penetration of a drug molecule and delay its elimination from the eye. The focus of this review is on the recent developments in topical ocular drug delivery systems, the rationale for their use, their drug release mechanism, and the characteristic advantages and limitations of each system. In addition, the review attempts to give various analytical procedures including the animal models and other models required for bioavailability and pharmacokinetic studies. The latter can aid in the design and predictive evaluation of newer delivery systems. The dosage forms are divided into the ones which affect the precorneal parameters, and those that provide a controlled and continuous delivery to the pre- and intraocular tissues. The systems discussed include: (a) the commonly used dosage forms such as gels, viscosity imparting agents, ointments, and aqueous suspensions; (b) the newer concept of penetration enhancers, phase transition systems, use of cyclodextrins to increase solubility of various drugs, vesicular systems, and chemical delivery systems such as the prodrugs; (c) the developed and under-development controlled/continuous drug delivery systems including ocular inserts, collagen shields, ocular films, disposable contact lenses, and other new ophthalmic drug delivery systems; and (d) the newer trends directed towards a combination of drug delivery technologies for improving the therapeutic response of a non-efficacious drug. The fruitful resolution of the above-mentioned technological suggestions can result in a superior dosage form for both topical and intraocular ophthalmic application⁵.

Srividya, B., et al., (2001), describes the formulation and evaluation of an ophthalmic delivery system of an antibacterial agent, ofloxacin,

based on the concept of pH-triggered *in situ* gelation. Polyacrylic acid (Carbopol 940) was used as the gelling agent in combination with hydroxypropylmethyl cellulose (Methocel E50LV) which acted as a viscosity enhancing agent. The developed formulation was therapeutically efficacious, stable, non-irritant and provided sustained release of the drug over an 8-h period. The developed system is thus a viable alternative to conventional eye drops⁹.

Kaur, I.P., et al., (2000), 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, HPMC), and by incorporating acetazolamide into 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* release pattern. The effect of these formulations on the IOP in normotensive conscious rabbits was also investigated. These formulations were found to be therapeutically effective with a peak effect at 2 h. 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 (MK-5). Results indicated that a topical effect of acetazolamide can be observed if the formulation (a) contains a suitable polymer to increase the residence time; (b) a penetration enhancer-as acetazolamide has a low permeability coefficient⁶ i.e. 4.

Vadnere, et al., (1984), studied a number of pluronic polyols with the aim of determining factors, which influence the transition temperature of the hydrogels. All the pluronic polyols studied showed endothermic enthalpy change for the sol-gel process²⁷.

Evaluations of *in-situ* gel system

The prepared *in-situ* gel formulations were evaluated for clarity, pH measurement, gelling capacity, drug content, rheological study, *in vitro* diffusion study, isotonicity, antibacterial activity, *in vivo* ocular testing in rabbits and accelerated stability studies. The pH of *in-situ* gel solution was found to be 7.4 for all the formulations. The formulation should have an optimum viscosity that will allow for easy instillation into the eye as a liquid (drops), which would undergo a rapid sol-to-gel transition (triggered by pH, temperature or ion exchange).

Physical parameters

The formulated *in-situ* gel solution is tested for clarity, pH, gelling capacity, and drug content estimation.

Gelling capacity

The gelling capacity of the prepared formulation is determined by placing a drop of the formulation in a vial containing 2.0 ml of freshly prepared simulated tear fluid and visually observed. The time taken for its gelling is noted^{7,28}.

Rheological studies

The viscosity measurements can be calculated using Brookfield viscometer, Cone and Plate viscometer. The *in-situ* gel formulations were placed in the sampler tube. From the literature it was evident that, the formulation before gelling should have a viscosity of 5 to 1000 mPas. And after ion gel-activation by the eye, will have a viscosity of from about 50-50,000 mPas^{10, 13}. The samples are analyzed both at room temperature at 25°C and thermostated at 37°C ± 0.5°C by a circulating bath connected to the viscometer adaptor prior to each measurement. The angular velocity of the spindle was increased 20, 30, 50, 60, 100, 200 and the viscosity of the formulation is measured. All the formulations exhibited Newtonian and pseudoplastic flow characteristics before and after gelling in the simulated tear fluid respectively^{6, 29}.

In vitro drug release studies

In vitro release study of *in-situ* gel solution was carried out by using Franz diffusion cell. The formulation placed in donor compartment

and freshly prepared simulated tear fluid in receptor compartment. Between donor and receptor compartment dialysis membrane is placed (0.22µm pore size). The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 1ml of sample is withdrawn at predetermined time interval of 1hr for 6 hrs and same volume of fresh medium is replaced. The withdrawn samples are diluted to 10ml in a volumetric flask with respective solvent and analyzed by UV spectrophotometer at respective nm using reagent blank. The drug content calculated using the equation generated from standard calibration curve. The % cumulative drug release (%CDR) calculated. The data obtained is further subjected to curve fitting for drug release data. The best fit model is checked for Krosmeiers Peppas and Fickian diffusion mechanism for their kinetics⁷.

Texture analysis

The consistency, firmness and cohesiveness of *in-situ* gel are assessed by using texture profile analyzer which mainly indicated gel strength and easiness in administration *in vivo*. Higher values of adhesiveness of gels are needed to maintain an intimate contact with mucus surface³⁰.

Isotonicity evaluation

Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. All ophthalmic preparations are subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the requisite viscosity. Formulations are mixed with few drops of blood and observed under microscope at 45X magnification and compared with standard marketed ophthalmic formulation³¹.

Drug-polymer interaction study and thermal analysis

Interaction study can be performed with Fourier Transform Infra Red (FTIR) spectroscopy. During gelation process the nature of the interacting forces can be evaluated using the technique by employing KBr pellet method. Thermo gravimetric Analysis (TGA) can be conducted for *in situ* forming polymeric system to quantitate the percentage of water in hydrogel. Differential Scanning calorimetry (DSC) conducted to observe if there are any changes in thermograms as compared with pure active ingredients used for gelation³⁰.

Antibacterial activity

The microbiological growth of bacteria is measured by concentration of antibiotics and this has to be compared with that produced by known concentration of standard preparation of antibiotic. To carryout microbiological assay serial dilution method is employed³².

Ocular irritancy test

The Draize irritancy test was designed for the ocular irritation potential of the ophthalmic product prior to marketing. According to the Draize test, the amount of substance applied to the eye is normally 100µl placed into the lower *cul-de-sac* with observation of the various criteria made at a designed required time interval of 1hr, 24hrs, 48 hrs, 72hrs, and 1week after administration. Three rabbits (male) weighing 1.5 to 2kg are used for the study. The sterile formulation is instilled twice a day for a period of 7 days, and a cross-over study is carried out (a 3 day washing period with saline was carried out before the cross-over study). Rabbits are observed periodically for redness, swelling, watering of the eye^{33, 34}.

Accelerated stability studies

Formulations are placed in ambient colour vials and sealed with aluminium foil for a short term accelerated stability study at 40±2 °C and 75±5% RH as per International Conference on Harmonization (ICH) states Guidelines. Samples are analyzed every month for clarity, pH, gelling capacity, drug content, rheological evaluation, and *in vitro* dissolution³¹.

Statistical analysis

The results obtained from the experiments of mucoadhesive strength and release studies were analysed statistically using multivariate tests. A statistically significant difference was conducted by using various SPSS software and difference was considered to be significant at $P < 0.05$.

CONCLUSION

Ophthalmic drug delivery system is burgeoning field in which most of the researchers are taking challenges to combat various problems related to this delivery. Steady advancement in the understanding of principles and processes governing ocular drug absorption and disposition and continuing technological advances have surely brought some improvements in the efficacy of ophthalmic delivery systems. The primary requirement of a successful controlled release product focuses on increasing patient compliance which the *in-situ* gels offer. Exploitation of polymeric *in-situ* gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the *in situ* gel dosage forms very reliable. Use of biodegradable and water soluble polymers for the *in-situ* gel formulations can make them more acceptable and excellent drug delivery systems³⁴⁻³⁵.

In-situ activated gel-forming systems seem to be favoured as they can be administered in drop form and produce appreciably less inconvenience with vision. Moreover, they provide better sustained release properties than drops. This type of dosage forms are used now a day in combat glaucoma, dry eye syndrome, Sjogren's syndrome, ARMD, trachoma etc.³⁶⁻³⁷.

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