IN SITU GELLING SYSTEM: NOVEL APPROACH FOR OPHTHALMIC DRUG DELIVERY

Rajeshwari N. Patil*, Rachana S.Kumar

Department of Pharmaceutics, MET’s Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik, 422 003 Maharashtra, India

Article Received on 30 April 2014, Revised on 25 May 2014, Accepted on 12 Jun 2014

ABSTRACT

Eye is the most vital organ of body. In ocular drug delivery the physiological constraints imposed by the protective mechanisms of the eye lead to low absorption of drugs, resulting in a shorter duration of the therapeutic effect. Conventional dosage forms (such as Eye drop, ointments, gels etc.) suffer from disadvantages like low residence time, blurred vision, frequent dosing. To overcome the limitations associated with conventional system, newer drug delivery system were developed. Newer research in ophthalmic drug delivery systems is directed towards a amalgamation of several drug delivery systems, that include to build up systems which not only prolong the contact time of the vehicle at the ocular surface, but also slow down the removal of the drug. In situ gels are in liquid phase while instillation but changed to gel in response to stimuli (which may be temperature, pH, ion, UV radiation). These stimuli also serve as basis for type of In situ gelling system. These systems not only help to increase in precorneal residence time of drug to a sufficient extent, so that drug can exhibit its maximum biological action but also decreases the systemic side effects to create a more pronounced effect with lower doses of the drug. Continuous delivery of drugs in a controlled manner to the anterior chamber of the eye will also eliminate the requirement for frequent drug administration, causing better patient compliance and thus serves as best alternative to conventional ophthalmic drops. In this article, an attempt has been made to highlight the important technical and pharmaceutically relevant concepts related with drug delivery systems developed for administration through the Ocular route.

Key words: Ophthalmic Delivery System, In-Situ Gel, Hydrogel, Phase Transition Systems.
INTRODUCTION
The current scenario of ophthalmic drug delivery is highly competitive and rapidly evolving. The conventional ocular drug delivery systems like solutions, suspensions and ointments show drawbacks such as increased precorneal elimination, high variability and blurred vision. Low absorption results in shorter duration of action, high frequency of eye drop instillation is associated with discomfort to the patient. Poor bioavailability of drugs from ocular dosage forms is mainly due to tear production, transient residence time and impermeability of corneal epithelium. Bioavailability, particularly for ocular solutions ranges from 1%-10% of total administered dose. This could be due to rapid precorneal kinetic resulting from reflex tearing and blinking. Inclusion of excess drug in formulation in an attempt to overcome bioavailability problems is potentially dangerous if drug solution drained from eye is systemically absorbed from nasolacrimal duct. The short pre-corneal contact time combined with corneal impermeability results in low bioavailability, and as a result, frequent dosing is usually needed.

OVERVIEW OF ANATOMY AND PHYSIOLOGY OF HUMAN EYE
The eye is vital organ of human body. The cornea, lens, and vitreous body are transparent media with no blood vessels. Oxygen and nutrients are transported to these nonvascular tissues by the aqueous humour. The aqueous humour has a high oxygen tension and about the same osmotic pressure as blood. The cornea also derives part of its oxygen need from the atmosphere and is richly supplied with free nerve endings. The transparent cornea is continued posterior into opaque white sclera, which consists of tough fibrous tissue. Both cornea and sclera withstand the intra-ocular tension constantly maintained in the eye. The eye is constantly cleansed and lubricated by the lachrymal apparatus, which consists of four structures: Lachrymal glands, lachrymal canals, lachrymal sac, naso- lachrymal duct. The lachrymal fluid secreted by the lachrymal glands is emptied on the surface of the conjunctiva of the upper eyelid at a turnover rate of 16% per min. It washes over the eyeball and is swept up by the blinking action of the eyelids. Thus the eyeball is continually irrigated by a gentle stream of lachrymal fluid that prevents it from becoming dry and inflamed. The lachrymal fluid in humans has a normal volume of 7µl and is an isotonic aqueous solution of bicarbonate and sodium chloride (pH 7.4) that serves to dilute irritants or to wash the foreign bodies out of the conjunctival sac. It contains lysozyme, whose bactericidal activity reduces the bacterial count in the conjunctival sac. The rate of blinking varies widely from one person
to another, with an average of approximately 20 blinking movements per min. During each blink movement the eyelids are closed for a short period of about 0.3 sec. [15]

Fig 1: Anatomy of Eye

Fate Of The Formulation Administered Through Ocular Route

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 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. This anatomy, physiology and biochemistry of the eye are responsible for the low bioavailability of drug. The challenge is to overcome these protective barriers of the eye without causing permanent tissue damage.[6, 12-15, 25]

Fig 2: Fate of the formulation administered through eye
This loss of drug is mainly due to drainage of the excess fluid by the naso-lacrimal duct, dilution, elimination of the solution by tear turn-over which results in a poor bioavailability of topically applied ophthalmic drugs. Various ways to reduce the effect of drainage and the dilution of the drug by the tears have been explored. They include the use of viscous and semi-solid vehicles act to increase corneal contact time to varying degrees but so far, no marked sustaining effect has been attained. They suffer from poor patient acceptance and difficulties in administration. These desired formulations should be a free-flowing liquid at room temperature to allow easily reproducible administration into the eye as a drop and should undergo in situ phase transition to form a strong gel that is capable of withstanding $^{[29]}$

---

**Fig 3:** Mechanism of generating physiological response of eye

---
Various Problems Encountered In Poor Bioavailability of Drugs Instilled Through Eye are: [6,7,12,28,29]

- Binding by the lacrimal proteins
- Drainage of the instilled solutions
- Lachrimation and tear turnover
- Limited corneal area and poor corneal penetration
- Non-productive absorption/adsorption;

Characteristics Required to Optimize Drug Delivery Systems: [4, 12, 15, 28, 29]

- Good corneal penetration
- Prolonged contact time with corneal tissue.
- Simplicity of installation for the patient.
- Non-irritative and comfortable form (the viscous solution should not provoke Lachrimation and reflex blinking)

IN-SITU GELLING SYSTEM

Two ways to circumvent disadvantages associated with conventional system are use of bioadhesive and phase transition systems which (1) can be either polymeric solutions or micro-particle suspensions. They are retained in the cul-de-sac by adhesive bonds established with the mucin or the epithelium. (2) Phase transition systems which are instilled in a liquid form and shift to the gel or solid phase once in the cul-de-sac. [8] Among these, the in situ gel-forming formulations seem to be a promising tool. [43, 45]

In-situ gelling systems are viscous, mucoadhesive, polymer-based liquids that exhibit sol-to-gel phase transition with its favourable residence time on the ocular surface due to change in a specific physico-chemical parameter like temperature, ionic strength, ultra violet irradiation or pH. The effective dose administered can be altered by increasing the retention time of medication into the eye by using in situ gel forming systems, thereby preventing the tear drainage. [5, 15-17, 28, 29] These systems can be injectable fluids that can be introduced into the body in a minimally invasive manner prior to solidifying or gelling within the desired tissue, organ, or body cavity. Injectable gel-forming matrices offer several advantages over systems shaped into their final form before implantation. When they are used to fill a cavity or a defect, their flowing nature enables a good fit. These have a characteristic property of temperature dependence, pH dependence and cation induced gelation. In situ gels are
administered by oral, ocular, rectal, vaginal, injectable and intra-peritoneal routes. Both natural and synthetic polymers can be used for the production of in situ gels. In situ-forming systems have been reported in the literature for various biomedical applications, including drug delivery, cell encapsulation, and tissue repair. The choice of a special Hydrogel depends on its intrinsic properties and envisaged therapeutic use. There is several possible mechanisms that lead to in situ gel formation: solvent exchange, UV-irradiation, ionic cross-linkage, pH change, and temperature modulation.

**Advantages of In-Situ Forming Gel**

- Less blurred vision as compared to ointment.
- Decreased nasolacrimal drainage of the drug which may causes undesirable side effects due to systemic absorption (i.e. reduced systemic side effects).
- The possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and moreover promoting precorneal retention
- Sustained, Prolonged drug release and maintaining relatively constant plasma profile.
- Reduced number/frequency of applications hence improved patient compliance and comfort.
- Generally more comfortable than insoluble or soluble insertion.
- Increased bioavailability due to Increased precorneal residence time and absorption

**Requirement of Ideal System**

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 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 compliance.

**Polymers**

Many natural, biodegradable, biocompatible and synthetic polymers like alginic acid, pluronic F127, xyloglucan, gellan gum, carbopol, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co- glycolide) and poly-caprolactone etc. are used in the preparation of in situ gelling system.
Table 1: Type of polymers used in In-situ gelling system

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermo sensitive polymers</td>
<td>Cellulose derivatives, Poloxamer, Poly (ethylene oxide)/Poly (D, L-lactic acid -co glycolic acid).</td>
</tr>
<tr>
<td>pH sensitive polymers</td>
<td>Carbopol, Cellulose acetophalate latex</td>
</tr>
<tr>
<td>Ionic cross linking polymers</td>
<td>Pectin, Alginic acid, Gellan gum</td>
</tr>
</tbody>
</table>

**Poloxamer**
It is thermo sensitive amphiphilic block copolymers, namely poly (ethylene oxide)–poly (propylene oxide)–poly (ethylene oxide) (PEO–PPO–PEO, poloxamers), have been extensively investigated as in situ forming gels. The most accepted mechanism to explain the thermogelification of poloxamers is that it results from interactions between different segments of the copolymer. The poloxamers copolymer molecules aggregate into micelles. An increase in the temperature leads to dehydration and conformational change that the hydrophobic chains regions, increasing chain friction and entanglement of the polymeric network. More unbound water is available at the hydrophilic regions of the gel; therefore, the external PEO chains interpenetrate extensively in the gel. At this point, gelation has occurred, and the micelles remain apparently intact and orderly packed, which has been described as “hard-sphere crystallization”. Though poloxamers are widely employed, they suffer from a major drawback of having weak mechanical strength, which leads to rapid erosion. One interesting approach, however, focuses on blends of poloxamers with other polymers like carbopol. [10, 15, 46]

**Carbopol**
It is Mucoadhesive polymer that increases the formulation’s mechanical strength, but also increases surface interaction with the ocular tissue and consequently contact time. Carbopol shows a solid-to-gel transition in aqueous solution as the pH is raised above its pKa of about 5.5; therefore, to have an easy administration, an acidic pH would be needed before carbopol phase transition. [43-46]

**Chitosan**
It is a biodegradable polymer that has demonstrated excellent ocular compatibility. It presents positively charged amine groups in its chemical structure that could interact with the negatively charged mucous layer, conferring a mucoadhesive characteristic. Chitosan solutions have been successfully used in prolonging contact time with the ocular surface.
Therefore, a combination of this polymer with poloxamers would be very promising for ocular administration, as the in situ mechanical strength of the formulation would be higher than that of both polymers alone. The result could be a prolonging of the contact time. [43-44]

In fact, specific blends of poloxamers and chitosan for the ocular delivery of timolol maleate were already studied. It is stated that these polymers can be used in combination to produce clear, sterile and non-irritating ophthalmic formulations.

**Mechanisms Of In Situ Gelation**

There are several possible mechanisms that lead to in situ gel formation: solvent exchange, UV-irradiation, ionic cross-linkage, pH change, and temperature modulation. The thermo sensitive approach can be advantageous for particular applications as it does not require organic solvents, co-polymerization agents, or an externally applied trigger for gelation. [19]

The solvent exchange approach consists of dissolving a water-insoluble polymer in a water-miscible, biocompatible solvent. Upon contact with body fluids, the solvent diffuses out of the polymer while water permeates the liquid polymer matrix. Due to its insolubility in water, the polymer precipitates, resulting in the formation of a solid polymeric implant. pH change approach deals with change in pH at site of administration. [12, 15, 19, 43-44]

**Approaches For In Situ Gelling Polymeric Drug Delivery System** [15-16, 20]

1) **Physiological stimuli approach**

a) **Temperature Induced In-Situ Gelling System:** The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach in situ formation. The ideal critical temperature range for such system is ambient and physiologic temperature. In these systems, gelling of the solution is triggered by change in temperature, thus sustaining the drug release. These hydrogels are liquid at room temperature (20 -25°C) and undergo gelation when in contact with body fluids (35- 37°C), due to an increase in temperature. [16] This is probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research which are able to swell or deswell as a result of changing in the temperature of the surrounding fluid.

Example: chitosan, pluronic, tetronics, xyloglucans, hydroxyl propylmethyl cellulose or hypromellose (HPMC). [20]

b) **pH induced in situ gel systems:** All the pH-sensitive polymers contain acidic or basic groups that either accept or release protons in response to changes in environmental pH.
Swelling of polymer increases as the external pH increases in the case of weakly acidic (anionic) groups also known as polyacids, but decreases if polymer contains weakly basic (cationic) groups termed as polybases. Sol to gel transition takes place when pH is raised from 4.2 to 7.4 (eye pH). At higher pH polymer forms hydrogen bonds with mucin which leads to formulation of hydrogen network. [12, 16, 20, 46]

Example: cellulose acetate phthalate (CAP) latex, carbopol, polymethacrilic acid (PMMA), polyethylene glycol (PEG), pseudolatexes. [20]

2) Physical change in biomaterial approach

a) Swelling mechanism: In situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space. One such substance is myverol (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures.

b) Diffusion mechanism: This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N- methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), tertahydrofuran, 2-pyrrolidone and triacetin has been shown to be useful solvents for such system.

3) Chemical reaction approach

a) Ionic cross linking: Certain ion sensitive polysaccharides undergo phase transition in presence of various ions such as K⁺, Ca²⁺, Mg²⁺, Na⁺. These polysaccharides fall into the class of ion-sensitive ones. [16] A novel ophthalmic vehicle, which gels in the presence of mono- or divalent cations present in the lacrimal fluids, was used as the gelling agent. [24] Formulation undergo liquid- gel transition under influence of an increase in ionic strength and gel formation take place because of complexation with polyvalent cations in lacrimal fluid. [12]

Example: Gelrite, gellan, hyaluronic acid, alginates [20]

b) Photo-polymerisation: A solution of monomers or reactive macromer and initiator can be injected into a tissues site and application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromers because they rapidly undergo photo polymerisation in the presence of suitable photo initiator. Photopolymerizable systems when
introduced to the desired site via injection get photocured in situ with the help of fiber optic cables and then release the drug for prolonged period of time\textsuperscript{[16]}

c) \textbf{Enzymatic cross-linking:} In situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydro gels that can release insulin have been investigated\textsuperscript{[16]}

\textbf{Principle Applications of In-Situ Gelling System}

\textbf{a) In Situ Forming Drug Delivery System for Parenteral Administration} \textsuperscript{[16, 47]}
Controlled parenteral systems used in drug delivery are implants, microspheres and liposomes. These suffer from limitations such as surgical implantation, complex manufacturing process, high production cost and drug leakage. Injectable in situ gel forming drug delivery system represents an attractive alternative to microspheres and implants as parenteral depot systems and has following advantages over conventional parenteral system:

\begin{itemize}
  \item Less invasive technique
  \item Direct delivery to a target area
  \item Biodegradable and biocompatible
  \item Economical
\end{itemize}

\textbf{b) In situ forming drug delivery system for ocular administration}
The poor bioavailability and therapeutic response exhibited by conventional ophthalmic dosage form (eye drops, eye gels, eye ointments) due to rapid precorneal elimination of the drug may be overcome by the use of a gel system instilled as drops into the eye and undergo a sol-gel transition in the cul de sac. For in situ gel based ocular delivery, natural polymers such as gellan gum, alginic acid and xyloglucan are most commonly used polymers. Local ophthalmic drug delivery has been used for various compounds such as antimicrobial agents, anti-inflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma. \textsuperscript{[16]}

c) \textbf{In situ forming drug delivery system for oral administration}
Pectin, xyloglucan and gellan gum are the natural polymers used for in situ forming oral drug delivery systems. The potential of an orally administered in situ gelling pectin formulation for
the sustained delivery of Paracetamol has been reported. The formulation consisted of gellan solution with calcium chloride and sodium citrate complex. When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of gellan thus forming a gel in situ. [16]

d) In situ forming drug delivery system for nasal administration
Gellan gum and Xanthan gum were used as in situ gel forming polymers. Animal studies were conducted using an allergic rhinitis model and the effect of in situ gel on antigen induced nasal symptoms in sensitised rats was observed [16]

e) In situ forming drug delivery system for rectal and vaginal administration
In situ gels also possess a potential application for drug delivery by rectal and vaginal route. Miyazaki et al. investigated the use of xyloglucan based thermo reversible gels for rectal drug delivery of Indomethacin. Administration of Indomethacin loaded xyloglucan based systems to rabbits indicated broad drug absorption peak and a longer drug residence time as compared to that resulting after the administration of commercial suppository [16]

Evaluation and Characterization of In-Situ Ophthalmic Gel [12, 15, 18, 20, 26-27, 31, 38-44]
1] Physical parameter [20, 12]
The formulated In-situ solution is tested for clarity, pH, gelling capacity, appearance.

a] Gelling capacity
Gelling capacity of prepared formulation can be determine by placing the drop of formulation in vial containing 2.0 ml of freshly prepared simulated tear fluid and visually observed. The time taken for gelling was noted.

b] Viscosity [20]
Viscosity can be calculated by using Brookfield viscometer, cone and plate viscometer. The In-situ gel formulation was placed in sampler tube. The samples are analyzed both at room temperature at 25 °c and thermo stated at 37 °c ± 0.5 °c by a circulating bath connected to viscometer adaptor prior to each measurement.

c] Clarity/ Appearance [21]
The clarity of formulated solutions determined by visual inspection under black and white background.
2] In vitro drug release studies\textsuperscript{12-13, 21}

In vitro drug release study of In-situ gel solution should be carried out by using Franz diffusion cell. Formulation placed in donor compartment and freshly prepared stimulated tear fluid in the receptor compartment. Between donor and receptor compartment dialysis membrane is placed. Then whole assembly is placed in thermostatically controlled magnetic stirrer. The temperature of medium was maintained at 37 °c ±0.5 °c. 1 ml of sample is withdrawn at predetermine time interval of 1 hr to 6 hr and same volume of fresh is replaced. The withdrawn sample is diluted to 10 ml of volumetric flask with respective solvent and analyzed by UV spectrophotometer at respective nm using blank reagent.

3] Drug content\textsuperscript{12-13, 21}

Is calculated using equation generated from standard calibration curve. The % cumulative drug release is calculated. The 1 ml of formulation was dissolved in 100ml of artificial tear fluid. The whole system was stirred on magnetic stirrer for 4-5 hr. From this solution the sample should be withdrawn and analyzed for UV for Drug content.

4] Texture analysis \textsuperscript{12, 13}

The consistency, firmness and cohesiveness of In situ gel are assessed by using texture profile analyzer which mainly indicates the gel strength and easiness in administration in vivo. The higher value of adhesiveness of gel needed to maintain an intimate contact with mucus surface.

5] Isotonicity evaluation\textsuperscript{12, 21}

Isotonicity is important characteristics of the ophthalmic preparation. Isotonicity has to be maintained to prevent tissue damage or irritation of eyes. Formulation is mixed with few drops of blood and observed under microscope at 42x magnification and compared with standard marketed ophthalmic preparation.

6] Interaction study\textsuperscript{12, 20, 21}

It was performed with Fourier Transform Infra Red (FTIR) spectroscopy. During gelation process the nature of interacting forces can be evaluated using the technique by employing Kbr Press Pellet method 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.
7] **Antibacterial/Antibiotic activity** [12, 13, 21]

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 antibiotics. To carry out microbiological assay serial dilution method is employed.

8] **The Draize irritancy test** [20]

It is 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 eyes is normally 25µl placed into the lower cul-de-sac with observation of the various criteria made at a designed required time interval of 1 hr, 24hrs, 45 hrs, 72 hrs and 1 week after administration. Three rabbits (male) weighing 1.5 to 2 kg 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.

9] **Accelerated stability studies** [12, 13, 20, 21]

Formulations are placed in ambient coloured vials and sealed with aluminium foil for a short terms 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 ability, drug content etc.

12] **Assay** [22]

An accurate amount of drug was dissolved in diffusion media of desired pH, and the absorbance of the resulting solutions was determined at nm. Drug content was calculated to estimate the percentage recovery of the loaded drug.

13] **Sol-gel Transition Temperature and Gelling time** [21]

For in situ gel forming systems incorporating thermo reversible polymers, the sol-gel transition temperature may be defined as that temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the time for first detection of gelation as defined above.

14] **Gel-strength** [21]

This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker, from the sol
form. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.

16] Viscosity and Rheology\[21\]
This is an important parameter for the in situ gels, to be evaluated. The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route of administrations) were determined with Brookfield rheometer or some other type of viscometers such as Ostwald's viscometer. The viscosity of these formulations should be such that no difficulties should encounter during their administration by the patient, especially during parenteral and ocular administration.

Commercial In-Situ Ophthalmic Products in Market\[16, 21\]
1] Timoptic-XE
It is a timolol maleate ophthalmic gel formulation of Merck and Co. Inc., supplied as a sterile, isotonic, buffered, aqueous gel forming solution of timolol maleate. This formulation is available in two dosage strengths 0.25% and 0.5% in market. The pH of the solution is approximately 7.0, and the osmolarity is 260-330 mOsm. Each ml of Timoptic-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Inactive ingredients include gellan gum, tromethamine, mannitol, and water for injection and the preservative used is benzododecinium bromide 0.012%. Timoptic-XE, when applied topically on the eye, reduces the elevated, as well as normal intraocular pressure, whether or not accompanied by glaucoma. \[21\]

2] AzaSite: Marketed product of In Site Vision. AzaSite is a topical ophthalmic solution of Azithromycin formulated in Dura Site (polycarbophil, edetate disodium, sodium chloride).

3] Akten: HPMC based gel of lidocaine hydrochloride for ocular surface anaesthesia. Akten also contains hypromellose, sodium chloride, and purified water as inactive ingredients. \[16\]

CONCLUSION
The introduction of in situ gelling systems has strengthened the link between therapeutic need and drug delivery. The In-situ ophthalmic gels provide number of advantages over conventional dosage forms like sustained and prolonged release of drug, good stability, biocompatibility, ease of instillation that makes this system very useful. These In-situ gels
can administered in drop form, so produces appreciably less inconvenience with vision. Use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems with minimum chances of irritation or nephrotoxicity. Moreover in situ gels have ease of commercialization which is added advantage from industrial point of view (Commercially available formulations prove this thing).

REFERENCES
4. Sawwalakhe HS, Maidankar JM, Channawar MA, Dr. Chandewar AV. Review Article On In Situ Gel Forming For Ocular Drug Delivery System. P.W. College of Pharmacy, Yavatmal, Amravati University.


