IJPSR (2012), Vol. 3, Issue 09 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 May, 2012; received in revised form 13 June, 2012; accepted 15 August, 2012

A NOVEL OPHTHALMIC DRUG DELIVERY SYSTEM: *IN-SITU* GEL

A.P. Patil*, A.A. Tagalpallewar, G.M. Rasve, A.V. Bendre, P.G. Khapekar

Sinhgad Institute of Pharmacy, Narhe, Pune - 411 041, Maharashtra, India

Keywords:
Phase transition system,
sustained release,
controlled release,
in-situ gel

Correspondence to Author:

Akash P. Patil

Sinhgad Institute of Pharmacy, Narhe,
Pune - 411 041, Maharashtra, India

E-mail: akashpatil1313@gmail.com

ABSTRACT

The ophthalmic *in-situ* gels now days proved an palpable sustained drug delivery in various eye diseases. The formulation of *in-situ* gels for eye which carries the advantages like easy for administration, reduces frequency of dose and improves patient compliance. The formation of *in-situ* gels depends on phase transition system or sol-gel transition system. The formulation approaches like temperature intonation, pH change and presence of ions from which the drug gets released in a sustained and controlled manner are utilised for *in-situ* gels. Various polymers that are used for the formulation of *in-situ* gels include chitosan, Pluronic F-127, poly-caprolactone, gellan gum, alginic acid, xyloglucan, pectin 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. The major problem encountered with topical administration is the rapid pre-corneal loss caused by nasolacrymal drainage and high tear fluid turnover which leads to only 10% drug concentrations available at the site of actions [1].

In the last decade, greater attention has been focused on development of controlled and sustained drug delivery systems. Many patents for their use in various biomedical applications including drug delivery have been reported [2]. Eye seems an ideal, easily accessible target organ for topical treatment. However the eye is in fact well protected against absorption of xenobiotics, first by the eyelids and tear-flow and then by the cornea, which forms the physical-biological barrier.

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 epithelium [3].

Most ocular treatments like eye drops and suspensions call for the topical administration of ophthalmic drugs to the tissues around the ocular cavity. These dosage forms are easy to instil but have the inherent drawback that the majority of the medication in them is immediately diluted. Extensive research has been carried in designing of polymeric drug delivery systems.

QUICK RESPONSE CODE

IJPSR:
ICV- 4.57

Website:
www.ijpsr.com

The development of *in-situ* gel systems has received considerable attention over the past few years and increasing number of *in-situ* gel forming systems have been investigated and in the tear film as soon as the eye drop solution is instilled into the *cul-de-sac* and is rapidly drained away from the pre-corneal cavity by constant tear flow and lacrimo-nasal drainage. For this reason, concentrated solutions and frequent dosing are required for the instillation to achieve an adequate level of therapeutic effect. One of the new classes of drug delivery systems, ophthalmic *in-situ* gels, which offer many advantages over conventional dosage forms, like increased ocular residence, possibility of releasing drugs at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf life [4, 5].

Barriers to Ocular Delivery Systems [6]

Blood-ocular barriers: The eye is protected from the xenobiotics in the blood stream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier shown in **figure 1 and table 1**. The anterior blood-eye barrier is composed of the endothelial cells in the uvea (The middle layer of the eye beneath the sclera. It consists of the iris, ciliary body, and choroid). This barrier prevents the access of plasma albumin into the aqueous humor, and also limits the access of hydrophilic drugs from plasma into the aqueous humor. The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space, but thereafter distribution into the retina is limited by the RPE and retinal endothelia.

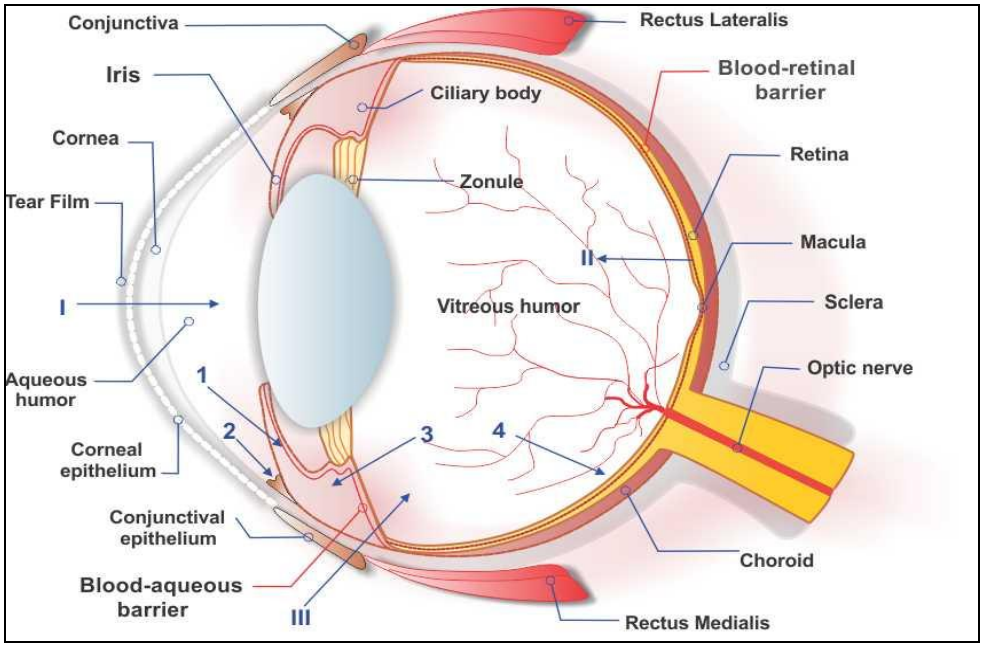

FIG. 1: BARRIERS IN OPHTHALMIC DRUG DELIVERY

TABLE 1: BARRIERS FOR THE OCULAR DELIVERY

	Conjunctiva	Cornea	Sclera
Surface area	17.65 ± 2.12 cm^2	1.04 ± 0.12	16 – 17
Thickness	-	0.57 mm	0.4 -0.5 mm
Structural Composition	Mucus membrane • Epithelium • Vasculature	5 layers • Epithelium • Bowman's membrane • Stomata	Collagen fibers • Water • Proteoglycans • Monopolysaccharids

Drug loss from the Ocular Surface: After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even though the lacrimal turnover rate is only about 1µl**/**min the excess volume of the instilled fluid is flown to the naso-lacrimal duct rapidly in a couple of minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may

take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.

Lacrimal fluid-eye barriers: Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions that limit the paracellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs. In general, the conjunctiva is leakier epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea.

Various approaches use to prepare *in-situ* Gel: There are different approaches reported for *in-situ* gels. An *in-situ* gelling system should be a low viscous, free flowing liquid to allow 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 prolonged the residence time of the gel formed *in-situ* along with its ability to release drugs in sustained manner which assist in enhancing the bioavailability, reduce systemic absorption and reduce the need for frequent administration leading to improved patient compliance [7].

Depending upon the method employed to cause sol to gel phase transition on the ocular surface; various approaches for the preparation of *in-situ* gel are recognized and given in **table 2**.

TABLE 2: VARIOUS APPROACHES FOR THE PREPARATION OF *IN-SITU* GEL

External stimuli	Mechanism	Examples of polymer
Temperature Dependent system	Formulation is liquid at room temperature(20-25°C) which undergoes gelation in contact with body fluid (35-37°C)	Poloxamer/Pluronics, Cellulose derivative
pH triggered system	Phase transition occur due to rise in pH from 4.2 to 7.4	Pseudolatexes, Carbomer(Acrylic acid) Cellulose acetate phthalate latex
Ion activated system	Formulation undergoes liquid-gel transition under influence of an increase in ionic strength	Chitosan, Gallen gum/ Gelrite, Alginate

- **Temperature dependent systems:** Temperature-sensitive *in-situ* gels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research [9]**.** The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature; is an attractive way to approach *in-situ* gels formation for ophthalmic drug delivery. Three main strategies exist in designing of thermo-responsive sol-gel polymeric system. For convenience, temperature-sensitive *in-situ* gels are classified into negatively thermo-sensitive, positively thermo-sensitive, and thermally reversible gels.

  Negative temperature-sensitive *in-situ* gels have a lower critical solution temperature (LCST) and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature are used for this purpose. Formulation is liquid at room temperature (20-25°C) which undergoes gelation in contact with body fluid (35-37°C). Temperature increases degradation of polymer chains which leads to formation of hydrophobic domains & transition of an aqueous liquid to *in-situ* gel [10-13].

- **pH dependent systems:** Formation of gel is induced by pH changes. All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of *in-situ* gel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups [14].

  The most of anionic pH-sensitive polymers are based on PAA (Carbopol, carbomer) or its derivatives. Sol to gel transition when pH rises from 4.2 to 7.4; at higher pH polymer forms hydrogen bonds with mucin which leads to formation of *in-situ* gel.

The formulation with pH-triggered *in-situ* gel is therapeutically efficacious, stable, non-irritant and provides sustained release of the drug for longer period of time than conventional eye drops. Pseudolatexes Carbomer (Acrylic acid) Cellulose acetate phthalate latex (CAP- Latex) Polyox are some of the examples of polymer used in pH-triggered *in-situ* gels.

- **Ion Activated Systems:** Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive polymers [15]. 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 agent [16].

Literature reviewed in the field of *in-situ* Gel: A literature describes a number of novel temperature, pH, and ion induced *in-situ* forming ophthalmic solutions. Each system has its own advantages and drawbacks. The selection of a particular *in-situ* gel depends on its intrinsic properties and therapeutic use.

Literature Review on Temperature dependent *In-Situ* Gels:

Giuseppina S, *et al.,* (2011), develop thermosensitive and mucoadhesive eye drops to maintain and prolong the contact of platelet lysate (PL) with corneal ulcers. A sterile vehicle based on chondroitin sulphate sodium (CS) and hydroxypropylmethyl cellulose (HPMC) was developed. An extemporaneous loading of the vehicle with PL was performed by them and the obtained formulation was able to quickly thermogelify at about 32°C and was characterized by good mucoadhesive properties.[17]

Manas B, *et al.,* (2011), developed and *in-vitro* evaluated ophthalmic thermo-sensitive *in-situ* gels of ketorolac, based on methylcellulose (MC) in combination with hydroxypropylmethyl cellulose (HPMC). The gel temperature of 1% MC solution was observed at 60°C. It was found that 6% oral rehydration salt without dextrose (ORS) was capable to reduce the gel temperature below physiological temperature. HPMC was added to increase viscosity and drug release time. The results indicated a large increase in viscosity at 37°C with addition of HPMC which provided sustained release of the drug over a 4 hour period. From *in-vitro* release studies, it has concluded that the developed systems were thus a better alternative to conventional eye drops [18].

Rathapon A, *et al.,*(2011), optimized and evaluated Pluronic F127-based thermoresponsive diclofenac sodium ophthalmic *in-situ* gels. They were prepared by cold method and investigated their physicochemical properties like sol–gel transition temperature, gelling capacity, rheological properties and effect of concentration of polymer i.e., carbopol 940, Pluronic-F68. An optimized formulation was selected and investigated its physicochemical properties before and after autoclaving, eye irritation potency in rabbits. *In vivo* ophthalmic absorption was performed in rabbits. It was found that physicochemical properties of diclofenac sodium *in-situ* gels were affected by formulation compositions. Increment of Pluronic-F127 content decreased sol–gel transition temperature of the products while increase in Pluronic-F68 concentration tended to increase sol–gel transition temperature. In this study, Carbopol 940 did not affect sol–gel transition temperature but it affected transparency, pH, and gelling capacity of the products. The optimized formulation exhibited sol–gel transition at 32.6±1.1°C with pseudoplastic flow behavior.[19]

Sirish V, *et al.,* (2010), prepared and evaluated novel *in-situ* ocular gelling system (Thermo-reversible gelling systems) of Ketorolac tromethamine. These gelling systems involve the use of Poloxamer as thermo reversible polymer and Methyl cellulose as release retardant. They evaluated the formulations for clarity, pH measurement, gelling capacity, drug content estimation, rheological study, *in vitro* drug release, ocular irritation studies (as per Draize test) and *ex-vivo* corneal permeation studies using isolated goats cornea. The developed formulations showed sustained release of drug for upto 5 hrs.[20]

Tais G, *et al.,* (2010), formulated an ophthalmic delivery system with improved mechanical and mucoadhesive properties that could provide prolonged retention time for the treatment of ocular diseases.

For this, they developed an *in-situ* forming gel comprised of the combination of a thermosetting polymer, poly (ethylene oxide)–poly (propylene oxide)–poly (ethylene oxide) (PEO–PPO–PEO, poloxamer), with a mucoadhesive agent (chitosan). Different polymer ratios were evaluated by oscillatory rheology, texture and mucoadhesive profiles. Scintigraphy studies in humans were conduced to verify the retention time of the formulations developed. The results showed that chitosan (0.25% and 0.5% w/v) improves the mechanical strength and texture properties of poloxamer (from 7% to 14% w/v) formulations and also confers mucoadhesive properties in a concentration-dependent manner. The study demonstrated that poloxamer/chitosan formulation in a concentration of 16/1.0% w/w showed an optimal gelation temperature (32 °C) and was able to withstand low shearing forces at 35 °C. The mechanical properties indicated that the formulation has a high hardness value (especially at 35°C). Gamma scintigraphy in humans confirmed a prolonged retention time of the poloxamer/chitosan 16:1 formulation in human eyes, 50–60% of the gel was still in contact with the cornea surface, which represents a fourfold increased retention in comparison with a conventional solution [21].

Indrajeet G, *et al.,*(2010), prepared and evaluated various *in-situ* gels of gatifloxacin prepared through use of sodium alginate and mucoadhesive polymers such as poloxamer 407, Carbopol 974P, and hydroxyethyl cellulose (HEC). They investigated the combined effect of two independent formulation variables in the preparation of *in-situ* gels by using a 3^2 factorial design. A surface plot was also created to graphically represent the effect of independent variables on the evaluation parameters. The developed formulations showed sustained release of drug for upto 6 hrs [22].

WenDi M, *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 co-polymer solution concentration increased. But the drug concentration had no obvious effect on drug release. The release rates of the drug from such co-polymer 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 conjunctiveal 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 system [23].

Cao Y, *et al.,*(2007), investigated a novel copolymer, poly (Nisopropylacrylamide) - 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 proved PNIPAAm-CS is a potential thermosensitive *in-situ* gel-forming material for ocular drug delivery, and it may improve the bioavailability, efficacy, and compliance of some eye drugs [24].

- **Literature Review on Ion Activated Gels**

Aparna B, *et al.,*(2011), formulated and evaluated an ophthalmic delivery system of an antiglaucoma agent, dorzolamide hydrochloride (2%w/v), based on the concept of ion-activated *in- situ* gelation. Sodium alginate (1 and 2 %w/v) was used as the gelling agent in combination with Hydroxy propyl Cellulose (0.1,0.2 and 0.3%w/v) that acted as a viscosity-enhancing agent. *In vitro* release studies indicated that the alginate**/**HPC solution retained the drug better than

the alginate or HPC solutions alone. The formulation were evaluated for *in vitro* diffusion studies, viscosity and intraocular pressure studies. The formulations were therapeutically efficacious, stable and provided sustained release of the drug over a period 10 hrs. These results demonstrate that the developed system is an alternative to conventional ophthalmic formulations.[25]

Gaur A, *et al.,*(2011), developed a novel Sodium Alginate *in-situ* gel system for sustained drug delivery and targeting. The *in-situ* gel formulation of Famotidine was prepared using Sodium Alginate as a gelling agent and calcium chloride as a source of cation. Different formulation were prepared using three different concentrations of Sodium Alginate (1.0, 1.5 and 2%), each with three different calcium chloride concentrations (0.05, 0.075 and 0.1%). *In Vitro* release studies were conducted in buffer (pH 7.4) and drug were analyzed by spectrophotometer. The *in-situ* gel containing 1.5% Sodium Alginate and 0.075% Calcium Chloride showed adequate release properties.[26]

Sirish V, *et al.,*(2010), formulated and evaluated the *in-situ* ocular gelling systems (ion activated gelling systems) of Ketorolac tromethamine. These gelling systems involve the use of Gelrite as polymer. They evaluated the formulation for clarity, pH measurement, gelling capacity, drug content estimation, rheological study, *in vitro* drug release, ocular irritancy studies (as per draize test) and ex-vivo corneal permeation studies using isolated goats cornea. The developed formulations showed sustained release of drug for upto 6 hrs. The formulations were found to be non-irritating with no ocular damage.[27]

Sindhu A, *et al.,* (2009), formulated and evaluated of an ophthalmic delivery system of an antibacterial agent ofloxacin, based on the concept of ion-activated *in situ* gelation. Sodium alginate was used as the gelling agent in combination with HPC (Hydroxy Propyl Cellulose) that acted as a viscosity-enhancing agent. *In vitro* release studies indicated that the alginate/HPC solution retained the drug better than the alginate or HPC solutions alone. The formulations were therapeutically efficacious, sterile, stable and provided sustained release of the drug over a period of time. These results demonstrate that the developed system is an alternative to conventional ophthalmic formulation.[28]

- **Literature review on pH dependent *in-situ* gels**

Rathore K, *et al.,* (2011), formulated and evaluated an *in-situ* ocular delivery system of an antiglaucomatous agent, timolol maleate, which is used in the treatment of primary open angle glaucoma, based on pH-triggered gelation. Poly acrylic acid was used as the gelling agent in combination with hypromellose, which acted as a viscolyzer. The developed formulation was therapeutically efficacious, non-irritant, stable and provided sustained release of the drug over a long period and shelf-life determined by Arrhenius equation was 1.6 years.[29]

Lekhraj V, *et al.,* (2010), the purpose of present work was to overcome these problems by developing an *in-situ* gel forming systems of flurbiprofen, based on the ion-activated and pH-induced *in-situ* gelation. *In-situ* gels of flurbiprofen were prepared by simple dispersion method using sodium alginate and carbopol along with HPMC and then evaluated for pH, gelling capacity, rheological, isotonicity, *in vitro* and *in vivo* studies. The developed formulations showed sustained release of drug for upto 5 hours [30].

Evaluation of *in- situ* Gel:

1. **Clarity:** The clarity of the formulations before and after gelling can be determined by visual examination of the formulations under light alternatively against white and black backgrounds [31].

2. **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 [32, 33].

3. **Ocular irritation studies:** 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 is 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 and rabbits are observed periodically for redness, swelling, watering of the eye [34].

4. **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 formulation.[35]

5. **Texture analysis:** The consistency, firmness and cohesiveness of *in-situ* gel is assessed by using texture profile analyzer which mainly indicated gel strength and easiness in administration *in vivo*. Higher values of adhesiveness of gels are needed to maintain an intimate contact with mucus surface [36].

   Texture analysis provides information on mechanical properties of samples, namely hardness, compressibility and adhesiveness. These properties can be directly correlated with sensory parameters *in vivo* and, therefore, are valuable in the development of a product with desirable attributes that contribute to patient acceptability and compliance.

   A formulation designed for ophthalmic use should be, for example, easily removed from the package, present a good spreadability on the corneal surface and adhere to the mucous layer without disintegrating, in order to prolong retention time [37].

6. ***In vitro* drug release studies:** *In-vitro* diffusion is generally evaluated by fabricated open flow through assembly (specially designed glass cylinder open at both ends) and semi-permeable cellophane membrane/dialysis membrane. Cellophane membrane, previously soaked overnight in simulated tear fluid is mounted by tied and sandwiched between the donor and receiver compartment.

   The 0.5 ml aliquot of donor solution is placed on top of cellophane membrane. Aliquots of medium (3.0 ml) are withdrawn at selected time intervals and replaced by 3.0 ml of freshly prepared simulated tear fluid through sampling port for analysis. The samples are diluted suitably and analyzed by UV spectrophotometer at specified wavelength [38].

7. ***Ex vivo* drug release studies:** Goat corneas are used to study the permeation across the corneal membrane. The cornea is carefully removed along with a 5-6 mm of surrounding scleral tissue and washed with cold saline. The washed corneas are kept in cold freshly prepared solution of tear buffer of pH 7.4. The study is carried out by using Franz-diffusion cell in such a way that corneum side is continuously remained in an intimate contact with formulation in the donor compartment.

   The receptor compartment is filled with STF pH 7.4 at $34^{o}C \pm 0.5^{o}C$. The receptor medium is stirred on a magnetic stirred. The samples are withdrawn at different time intervals and analyzed for drug content. Receptor phase is replenished with an equal volume of STF (pH 7.4) at each time interval [39].

8. ***In vivo* Scintigraphy Studies:** Gamma scintigraphy is a well-established technique for in vivo evaluation of ophthalmic retention time. Although the rabbit is the commonly recommended animal model for ophthalmic formulations evaluation, human volunteers are preferred for this study due to physiological differences between rabbits and humans, especially the blinking rate [40].

9. **Accelerated Stability Studies:** Formulated gel preparations are kept at different temperature conditions like 25°C to 28°C ambient temperature (temperature in the working area), 4±1°C (refrigerated temperature) and 37±2°C (temperature in the incubator) for 6 week. The following parameters of the gel such as colour, consistency, drug content and degradation rate constant (K) are studied. To assess the shelf life, the samples are subjected to stability studies. Selected sterilized formulations are stored at 4±1°C (refrigerated temperature), 37±1°C (ambient temperature) and

45±1°C (extreme temperature) for a period of 3 months and analyzed at intervals of 7, 14, 28, 42, 60 and 90 days. The formulations are evaluated at periodic intervals for drug content (by UV Spectrophotometer), clarity, pH, sol-gel transition, rheology, *in-vitro* drug release and sterility [41].

CONCLUSIONS: Ophthalmic drug delivery system is burgeoning field in which most of the researchers are taking challenges to combat various problems related to this delivery. The primary requirement of a successful controlled release product focuses on increasing patient compliance which the *in-situ* gels offer. The use of polymeric *in-situ* gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Use of biodegradable and water soluble polymers for the *in-situ* gels formulations can make them more acceptable and excellent drug delivery systems.

REFERENCES

1. Sirish V, Sadhna K, and Nalini S: Formulation and evaluation of ion activated ocular gels of ketorolac Tromethamine. International Journal of Current Pharmaceutical Research 2010; 2:33-38.
2. Shall J: Recent trends in ophthalmic drug delivery. International Journal of Pharmaceutics 1982; 241: 47-55.
3. Rathore K and Nema R: Review on Ocular inserts. International Journal Pharmaceutical Technology and Research 2009; 1:164-169.
4. Patel D, Patel M and Patel N: Preparation and evaluation of ocular inserts containing brimonidine tartrate. International Journal of Pharmaceutics and Research 2009; 1:19-22.
5. Aggarwal D and Kaur I: Improved pharmacodynamics of timolol maleate from a mucoadhesive niosomal ophthalmic drug delivery system. International Journal of Pharmaceutics 2005; 290**:**155-169.
6. Urtti A: Challenges and obstacles of ocular pharmacokinetics and drug delivery. Advanced Drug Delivery Reviews 2006; 58: 1131-1135.
7. Indu P, Manjit S and Meenakshi K: Formulation and evaluation of ophthalmic preparations of acetazolamide. International Journal of Pharmaceutics 2000; 199:119-127.
8. Basavaraj K, Manvi F and Manjappa A: Review *In-situ* forming hydrogels for sustained ophthalmic drug delivery. Journal of Control Release 2007; 122: 119-134.
9. Hongyi Q and Wenwen C: Development of a poloxamer analogs/carbopol-based *in- situ* gelling and mucoadhesive ophthalmic delivery system for puerarin. International Journal of Pharmaceutics 2007; 337:178-187.
10. Annick L: The use of mucoadhesive polymers in ocular drug delivery. Advanced Drug Delivery Reviews 2005; 57:1595-1639.
11. Lin C and Metters A: Hydrogels in controlled release formulations: Network design and mathematical modelling. Advanced Drug Delivery Reviews 2006; 58: 1379-1408.
12. Tomme S, Storm G and Hennink E: *In-situ* gelling hydrogels for pharmaceutical and biomedical applications. International Journal of Pharmaceutics 2008; 355: 1-18.
13. Qiu Y and Park K: Environment-sensitive hydrogels for drug delivery. Advanced Drug Delivery Reviews 2001; 53:321-339.
14. Balasubramaniam J, Kant S and Pandit J: *In vitro* and *in vivo* evaluation of the Gelrite gellan gum-based ocular delivery system for indomethacin. Acta Pharma 2003; 53: 251-261.
15. Johan C, Katarina E, Roger P and Katarina J: Rheological evaluation of gelrite *in-situ* gel for opthalmic use. European Journal of Pharmaceutical Sciences 1998; 6: 113-116.
16. Giuseppina S, Maria C, Silvia R, Franca F and Michela M: Thermosensitive eyedrops containing platelet lysate for the treatment of corneal ulcers. International Journal of Pharmaceutics 2012; 426: 1-6.
17. Manas B, Sanchita D, Dipankar C and Lakshmi K: *In-Situ* Gels for Ocular Delivery. Science Pharm. 2011; 79:352-358.
18. Rathapon A and Suthira T: Optimization and evaluation of thermoresponsive diclofenac sodium ophthalmic *in-situ* gels. International Journal of Pharmaceutics 2011; 411: 128-135.
19. Sirish V and Sadhna K: Development and evaluation of thermoreversible ocular gels of ketorolac tromethamine. International Journal of Biopharmaceutics 2010; 1: 39-45.
20. Tais G and Guilherme M: A poloxamer/chitosan *in situ* forming gel with prolonged retention time. European Journal Pharmaceutics and Biopharmaceutics 2010; 75:186-193.
21. Indrajeet D, Amrit B, Trushali S, Avinash H and Rajesh N: Use of factorial design in formulation and evaluation of ophthalmic gels of gatifloxacin: Comparison of different mucoadhesive polymers. Drug Discoveries & Therapeutics 2010; 4: 423-434.
22. Wen D, Hui X, Chao W, Shu-Fang N and Wei-San P: Pluronic F127-g-poly(acrylic acid) copolymers as *in situ* gelling vehicle for ophthalmic drug delivery system. International Journal of Pharmaceutics 2008; 350:247-256.
23. Cao Y, Zhang C, Shen W, Cheng Z, Yu LL and Ping Q: A Poly (N-isopropyle acrylamide)-chitosan as thermosensitive *in situ* gel forming sistem for ocular drug delivery 2007; 120: 186-194. Journal of Control Release 2007; 120:186-194.
24. Aparna B and Sitanshu S: *In-situ* gelling ophthalmic drug delivery system for glaucoma. International Journal of Pharmaceutics and Bio Sciences 2011; 2: 7-14.
25. Gaur A and Saraswat R: Formulation and evaluation of Sodium Alginate Based *In-Situ* gel Drug Delivery System of Famotidine. International Journal Research Article Pharmaceutical Innovations 2011; 1: 100-109.
26. Sirish V, Sadhna K and Nalini S: Formulation and evaluation of ion activated ocular gels of ketorolac Tromethamine. International Journal of Current Pharmaceutical Research 2010; 2: 54-62.
27. Sindhu A and sharon F: Sustained ophthalmic delivery of ofloxacin from an ion-activated *in situ* gelling system. Pakistan Journal of Pharmaceutical Sciences 2009; 22: 175-179.
28. Rathore K and Nema R: Management of Glaucoma: a review. International Journal of Pharmaceutical Technology and Research 2009; 1: 863-869.
29. Lekhraj V, Mohammad S, Navdeep S and Ritu S: Development of phase change solutions for ophthalmic drug delivery based on ion activated and pH induced polymer. International Journal of pharmaceutical professional's research 2010; 1:75-82.
30. Mitan R, Gokulgandhi R, Megha B and Dharmesh M: A pH triggered *in-situ* gel forming ophthalmic drug delivery system for tropicamide. Drug Delivery Technology 2007; 5: 44-49.

31. Pandit D, Bharathi A and Singh S: Long acting ophthalmic formulation of indomethacin: Evaluation of alginate gel systems. Indian Journal of Pharmaceutical Sciences 2007; 69: 37-40.
32. Doijad R, Manvi F and Malleswara R: Sustained ophthalmic delivery of gatifloxacin from *in-situ* gelling system. Indian Journal of Pharmaceutical Sciences 2006; 68: 814-818.
33. Sautou V, Labret F, Grand A, Gellis C and Chopineau J: Impact of deep-freezing on the stability of 25 mg/ml vancomycin ophthalmic solutions. International Journal of Pharmaceutics 2002; 234:205-207.
34. Jones D, Lawlor M and Woolfson A: Examination of the flow rheological and textural properties of polymer gels composed of poly(methylvinylether-comaleic anhydride) and poly(vinylpyrrolidone): rheological and mathematical interpretation of textural parameters. Journal of Pharmaceutical Sciences 2002; 91: 2090-2101.
35. Jones D, Woolfson A and Brown A: Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels composed of cellulose polymers. International Journal of Pharmaceutics 1997; 151: 223-233.
36. Jain G, Jain N, Pathan S, Akhter S, Talegaonkar S and Chander P: Ultra high pressure liquid chromatographic assay of moxifloxacin in rabbit aqueous humor after topical instillation of moxifloxacin nanoparticles. Journal of Pharmaceutics and Biomedical Analysis 2010; 52:110-113.
37. Mohanambal E, Arun K and Abdul H: Formulation and Evaluation of pH-triggered *in situ* Gelling System of Levofloxacin. Indian Journal of Pharmaceutical Education and Research 2011; 45: 58-64.
38. Sirish V, Sadhna K and Nalini S: Development and evaluation of thermoreversible ocular gels of Ketorolac Tromethamine. International Journal of Biopharmaceutics 2010; 1: 39-45.
39. Rittenhouse KD and Pollack GM: Microdialysis and drug delivery to the eye, Advance Drug Delivery Reviews 2000; 45: 229-241.
40. Urtti A, Pipkin J, Rork G and Repta A: Controlled drug delivery devices for experimental ocular studies with timolol *in vitro* release studies, International Journal of Pharmaceutics 1990; 61: 235-240.

How to cite this article:
Patil A.P., Tagalpallewar A.A., Rasve G.M., Bendre A.V., and Khapekar P.G.: A Novel Ophthalmic Drug Delivery System: *In-Situ* Gel. *Int J Pharm Res Sci*. 3(9); 1000-1008.