JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

pH Sensitive in Situ Ocular Gel: A Review

Chand Suresh*, Sharma Abhishek

Department of Pharmaceutics, L.R. Institutes of Pharmacy, Solan,H.P., India-173223

ABSTRACT:

Eye is the most vital organ of the body.Eye suffer from various eye problems like glaucoma, endopthalmitis, dry eye syndrome, trachoma, keratitis, conjunctivitis etc. To achieve effective ocular therapy, an adequate amount of active ingredients must be delivered and maintain at the site of action within the eye.To improve ophthalmic drug bioavailability, there are considerable efforts directed towards newer drug delivery systems for ophthalmic administration. Since Conventional delivery systems often result in poor bioavailability and therapeutic response because of high tear fluids turn over and dynamics cause rapid elimination of the drug from the eyes. Newer research in ophthalmic drug delivery systems is directed towards a 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 *Insitu* gel, collagen shield, minidisc, ocular film, ocusert, nanosuspension, nanoparticulate system, liposomes, niosomes, dendrimers, ocular iontophoresis etc.So, to overcome bioavailability problems, ophthalmic in situ gels were developed. This review also summarizes various temperature, pH, and ion induced *in-situ* forming polymeric systems used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability thus optimizing ocular therapy.

KEY WORDS: In situ gels, pH-triggered *Insitu* system, Ion-activated *Insitu* system, Temperature evident *Insitu* system.

Article history:

Received 22 July 2016
Revised 26 July 2016
Accepted 16 Aug 2016
Available online 01 Sept 2016

Citation:
Citation:

Chand Suresh*, Sharma Abhishek pH Sensitive in Situ Ocular Gel: A Review **J Pharm Sci Bioscientific Res**. 2016. 6(5):684-694

For Correspondence:
Suresh Chand
Department of Pharmaceutics, L.R. Institutes of Pharmacy, Solan-173223,H.P., India.

(www.jpsbr.org)

INTRODUCTION:

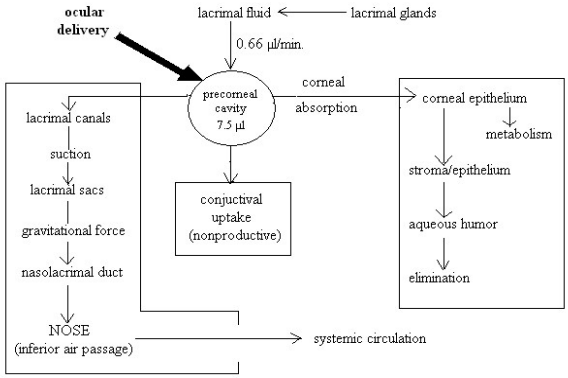
In the development of ocular drug delivery system lot of complications and difficulties are found. The conventional drug delivery such as suspension, ointment, solution show some drawbacks like increase pre-corneal drainage, blurred vision, low bioavailability low residence time. Various problems encountered in poor bioavailability of the eye installed drugs are:

- Binding by the lachrymal proteins,
- Drainage of the instilled solutions,
- Lachrimation and tear turnover,
- Limited corneal area and poor corneal metabolism,
- Non-productive absorption/adsorption1,

Although various formulation exists in market for ocular drug delivery but are not able to provide highest bioavailability related to administered dose. Whenever an ophthalmic drug is applied through a conventional dosage form to the anterior segment of the eye, only small amount (5%) actually

penetrates the cornea and reaches the interior tissue of the eyes. Factors that affects drug bioavailability includes rapid solution drainage by gravity, induced lachrymation, blinking reflex, normal tear turnover, superficial absorption of drug into the conjunctiva and sclera, rapid removal by the peripheral blood flow and low corneal permeability (act as lipid barrier). The progress has been made in gel technology for the development of droppable gel. They are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco-elastic gel and this provides a response to environmental changes[2].

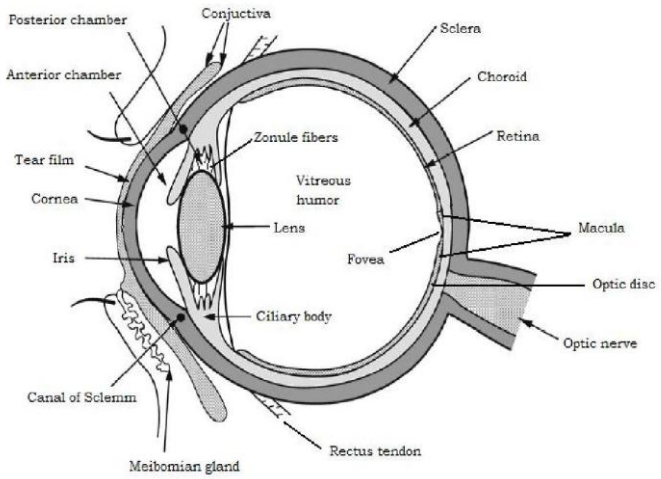
Systemic absorption of the drug drained through the nasolacrimal duct may result in some undesirable side effects. To overcome these problems ophthalmic in situ gels have been investigated in an attempt to extend the ocular residence time of medications for topical application to the eye[3].



Routes of ocular absorption of drugs.

In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs. These polymers undergo sol gel transition, once administered. From the early 1970's natural and synthetic polymers began to be investigated for controlled release formulation. The advantages of using biodegradable polymers in clinical applications are apparent. Various natural and synthetic polymers are used for formulation development of in situ common drug delivery systems[4].

The unique anatomy, physiology and biochemistry of eye offer many challenges to developing effective ophthalmic drug delivery systems. Topical delivery into cul-de-sac is, by far the most common route of ocular drug delivery[5].



Structure of the Eye[6]

Insitu Gelling system[7]

This novel drug delivery system promotes the importantly ease and convenience of administration, deliverance ofaccurate dose as well as to prolong residence time of drugin contact with mucosa, that problems generally encountered in semisolid dosage forms. In situ-gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered. From the early 1970's natural and synthetic polymers began to be investigated for controlled release formulations. The advantages of using biodegradable polymers in clinical applications are apparent. Various natural and synthetic polymers are used for formulation development of in situ forming drug delivery systems.

Approaches of In Situ Gel Drug Delivery[7]**:**

There are four broadly defined mechanisms used for triggering the in situ gel formation of biomaterials:

- Physiological stimuli (e.g., temperature and pH),

- Physical changes in biomaterials (e.g., solvent exchange and swelling),

 Chemical reactions (e.g., enzymatic, chemical and photo-initiated polymerization).

1. In situ formation based on physiological stimuli

Thermally trigged system

Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. The use of a 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, such that clinical manipulation is facilitated and no external source of heat other than that of body is required for trigger gelation. A useful system should be tolerable to account for small differences in local temperature, such as might be encountered in appendages at the surface of skin or in the oral cavity. Three main strategies are exists in engineering of thermoresponsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels.

Negative temperature-sensitive hydrogels 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 is used for this purpose. One of the most extensively investigated polymers that exhibit useful LCST transition is poly(N-isopropyl acrylamide) (PNIPAAm). PNIPAAm is a water soluble polymer at its low LCST, but hydrophobic above LCST, which result on precipitation of PNIPAAm from the solution at the LCST. Pluronics are poly (ethylene oxide)-poly (propyleneoxide)-poly (ethylene oxide) (PEO-PPOPEO) triblock copolymer that are fluid at low temperature, but forms thermo responsible gel when heated as a consequences of a disorder-order transition in micelle packing which makes these polymers suitable for in situ gelation. A positive temperature sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate) have positive temperature dependence of swelling. The most commonly used thermoreversible gels are these prepared from poly(ethylene oxide)-b-poly(propylene oxide)-bpoly(ethylene oxide) (Pluronics®, Tetronics®, poloxamer). Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature. Novel “protein polymers” called as ProLastins, which undergo an irreversible sol gel transition, when injected as asolution into the body, the material forms a firm, stable gel within minutes. It remains at the site of injection providing absorption times from less than one week to many months. Such a system would be easy to administer into desired body cavity.

pH triggered systems

Another formation of in situ gel based on physiologic stimuli is 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 hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The most of anionic pH sensitive polymers are based on PAA (Carbopol®,carbomer) or its derivatives. Likewise poly vinyl acetal diethyl amino acetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition. Drug formulated in liquid solutions have several limitations including limited bioavailability and propensity to be easily removed by tear fluid. To minimize this factors and maximize this drug delivery by making a poly(acrylic acid) (PAA) solution that would be gel at pH 7.4, by that we found that at concentrations high enough to cause gelation, however, the low pH of PAA solution would cause damage to surface of eye before being neutralized by the lacrimal fluid. This problem was solved by partially by combining PAA with HPMC, a viscous enhancing polymer, which resulted in pH responsive polymer mixtures that was sol at pH 4 and gel at pH 7.4. Mixtures of poly(methacrylic acid) (PMA) and poly(ethylene glycol) (PEG) also has been used as a pH sensitive system toachieve gelation.

2. In situ formation based on physical mechanism Swelling

In situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space. One such substance is myverol 18-

99 (glycerol mono-oleate), which is polar 1400 lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some Bioadhesive properties and can be degraded in vivo by enzymatic action.

Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. Nmethyl-pyrrolidone (NMP) has been shown to be useful solvent for such system.

3. In situ formation based on chemical reactions

Chemical reactions that results in situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

Ionic cross linking

Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones .While k-carrageenan forms rigid, brittle gels in reply of small amount of K+, icarrageenan forms elastic gels mainly in the presence ofCa2+. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na+. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca2+. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca2+ due to the interaction with glucuronic acid block in alginate chains.

Enzymatic cross-linking

In situ formation catalysed 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 hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation.

Photo-polymerisation

Photo-polymerisation is commonly used for in situ formation of biomaterials. A solution of monomers or reactive macromer and initiator can be injected into a tissues site and the 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 photopolymerisation in the presence of suitable photoinitiator. Typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet is not used often because it has limited penetration of tissue and biologically harmful. A ketone, such as 2,2- dimethoxy-2-phenyl acetophenone, is often used as the initiator for ultraviolet photo-polymerization, where as camphorquinone and ethyl eosin initiators are often used in visible light systems. These systems can be designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence in vivo. Photo polymerizable systems when introduced to the desired site via injection get photocured insitu gel with the help of fiber optic cables and then release the drug for prolonged period of time. The photo-reactions provide rapid polymerization rates at physiological temperature. Furthermore, the systems are easily placed in complex shaped volumes leading to an implant formation.

: **Classification of *Insitu* Polymeric System**[9]

Pectin

Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α-(1-4)-Dgalacturonic acid residues. Low methoxypectins (degree of esterification <50%) readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains in a manner described by egg-box model . Although the gelation of pectin will occur in the presence of H + ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery. The main advantage of using pectin for these formulations is that it is water soluble, so organic

solvents are not necessary in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is administered orally. Calcium ions in the complexed form may be included in the formulation for the induction of pectin gelation. Sodium citrate may be added to the pectin solution to form a complex with most of calcium ions added in the formulation. By this means, the formulation may be maintained in a fluid state (sol), until the breakdown of the complex in the acidic environment of the stomach, where release of calcium ions causes gelation to occur. The quantities of calcium and citrate ions may be optimized to maintain the fluidity of the formulation before administration and resulting in gelation, when the formulation is administered in stomach. The potential of an orally administered in situ gelling pectin formulation for the sustained delivery of Paracetamol has been reported.

Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D-xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. When xyloglucan is partially degraded by β- galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod like chains. The sol-gel transition temperature varies with the degree of galactose elimination. It forms thermally reversible gels on warming to body temperature. Its potential application in oral delivery exploits the proposed slow gelation time (several minutes) that would allow in-situ gelation in the stomach following the oral administration of chilled xyloglucan solution. Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular and rectal drug delivery.

Gellan gum

Gellan gum (commercially available as Gelrite TM or Kelcogel TM) is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It has the tendency of gelation which is temperature dependent or cations induced. This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water. 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. In situ gelling gellan formulation as vehicle for oral delivery of theophylline is reported.

Alginic acid

Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages . The proportion of each block and the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form firm gels on addition of di- and tri- valent metal ions by a cooperative process involving consecutive glucuronic residues in the α-Lglucuronic acid blocks of the alginate chain. Alginic acid can be chosen as a vehicle for ophthalmic formulations, since it exhibits favourable biological properties such as biodegradability and nontoxicity. A prolonged precorneal residence of formulations containing alginic acid was

looked for, not only based on its ability to gel in the eye, but also because of its mucoadhesive properties.

Xanthum gum

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β- D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronicacid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain.

Chitosan

Chitosan is a biodegradable, thermosensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. The pH gelling cationic

polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution.

Carbopol

Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution, while reducing the acidity of the solution. Various water soluble polymers such as carbopol system, hydroxy propyl methyl cellulose system, poly(methacrylic acid)- poly(ethylene glycol) come under the category of pHinduced in-situ precipitating polymeric systems. Based on this concept, the formulation and evaluation of an ophthalmic delivery system for indomethacin for the treatment of uveitis was carried out. A sustained release of indomethacin was observed for a period of 8 h in vitro thus considering this system as an excellent candidate for ocular delivery.

Pluronic F-127

Poloxamers or pluronic (marketed by BASF Corporation) are the series of commercially available difunctional triblock copolymers of non-ionic nature. They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the blocks of relatively hydrophilic poly ethylene oxide. Due to the PEO/PPO ration of 2:1, when these molecules are immersed into the aqueous solvents, they form micellar structures above critical micellar concentration. They are regarded as PEOPPO- PEO copolymers. Chemically they are Oxirane, methyl-, polymer with oxirane or α-Hydro-ω- hydroxypoly(oxyethylene)a poly(oxypropylene)b poly(oxyethylene)a block copolymer. The pluronic triblock copolymers are available in various grades differing in molecular weights and physical forms. Depending upon the physical designation for the grades are assigned, as F for flakes, P for paste, L for liquid. Pluronics or Poloxamers also undergo in situ gelation by temperature change. They are triblock copolymers consisting of poly(oxyethylene) and poly(oxypropylene) units that undergo changes in solubility with change in environment temperature. Pluronic™ F127. A 25-40% aqueous solution of this material will gel at about body temperature, and drug release from such a gel occurs over a period of up to one week. Pluronic F-127 was used as an in situ gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxy propyl methyl cellulose to ensure long residence time at the application site.

Controlled release of drug was achieved in-vitro indicating antimycotic efficacy of developed formulation for a longer period of time.

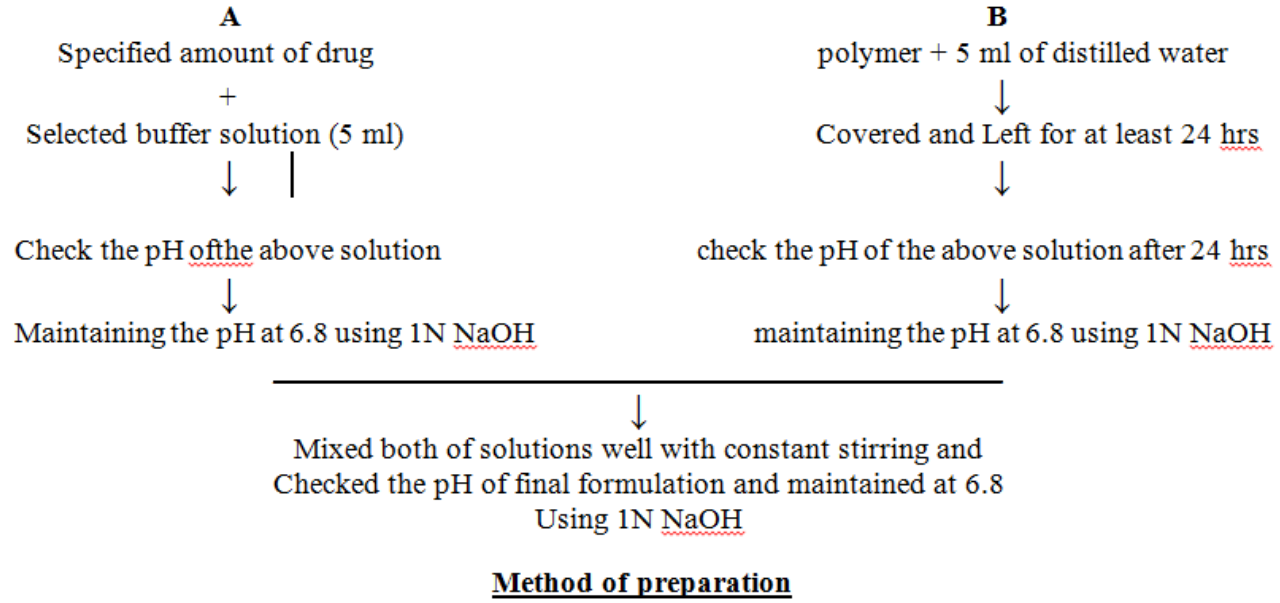
Synthetic polymers

Synthetic polymers are popular choice mainly for parenteral preparations. The trend in drug delivery technology has been towards biodegradable polymers, requiring no follow up surgical removal, once the drug supply is depleted. Aliphatic polyesters such as poly(lactic acid), poly(glycolic acid), poly(lactide-coglycolide), poly(decalactone), poly-ε-caprolactone have been the subject of the most extensive recent investigations. Various other polymers like triblock polymer systems

composed of poly(D,L-lactide)-block poly(ethylene glycol), block poly(D,L-lactide), blends of low molecular weight poly(D,L-lactide) and poly(ε-caprolactone) are also in use. These polymers are mainly used for the injectable in situ formulations. The feasibility of lactide/glycolide polymers as excipients for the controlled release of bioactive agents is well proven. These materials have been subjected to extensive animal and human trials without evidence of any harmful side effects. When properly prepared under GMP conditions from purified monomers, the polymers exhibit no evidence of inflammatory response or other adverse effects upon implantation. Another type of synthetic polymeric system includes the in situ crosslinked system, where the polymers form cross linked networks by means of free radical reactions that may occur by means of light (photopolymerizable systems) or heat (thermosetting systems). Thermosetting systems are in the sol form when initially constituted, but upon heating, they set into their final shape. This sol-gel transition is known as curing. But if this cured polymer is heated further, it may lead to degradation of the polymer. Curing mainly involves the formation of covalent cross links between polymer chains to form a macromolecular network. Dunn et al. designed a thermosetting system using biodegradable copolymers of DL-lactide or L-lactide with ε-caprolactone for prosthetic implant and slow

release drug delivery systems. This system is liquid outside the body and is capable of being injected by a syringe and needle and once inside the body, it gels. In insitu precipitating polymeric systems, thepolymer precipitation from solution may lead to gel formation in situ and this precipitation can be induced by change in temperature (thermosensitive systems), solvent removal or by change in pH. An important example of thermosensitive polymer is poly-(N-isopropyl acrylamide), [poly (NIPAAM)], which is used for the formation of in situ gels. It has lower critical solution temperature phase separation at about 32. The polymers such as poly(DLlactide), poly(DL-lactideco-glycolide) and poly(DL-lactideco-Ξ-caprolactone) form solvent-removal precipitating polymeric system.

METHOD OF PREPARATION (pH triggered method):-



Method of preparation

EVALUATION PARAMETERS:

PHYSICAL APPEARANCE: Physical appearance of the formulations was visually observed .

pH: The pH of the prepared in situ gelling system after addition of all the ingredients was measured using pH meter. pH of all the formulations were adjusted to 7.4 [8,9]

CLARITY: The clarity of the all formulations before and after gelling is to be determined by visual inspection of the formulations under light, alternatively against white and black backgrounds[9,10.]

GELLING CAPACITY TEST: Gelling capacity of the representative formulations was determined by placing a drop of the sample into a test tube containing 2ml of pH 7.4 simulated tear fluid (STF) equilibrated at 35±1◦C. The visual assessment of gel formation and dissolution with time record was performed in triplicate[11].

DRUG CONTENT: The drug content of formulation was determined by taking 1 ml of the formulation and diluting it to 10 ml with STF was determined at 320 nm by using UV-Visible spectrophotometer[12].

VISCOSITY: Viscosity of the instilled formulation is an important factor in determining residence time of drug in the eye. The solutions were allowed to gel in the STF and then the viscosity determinations were carried out by using Brooke field viscometer, angular velocity ran from 10-100 rpm. Viscosity of the formulations increased with increase in polymer concentration. The hierarchy of shear rate was reversed and average of two readings was used to calculate viscosity[13].

IN VITRO RELEASE STUDIES:

In vitro release studies of in-situ gel were performed by dialysis tubing cellophane membrane using. Cellophane membrane, previously soaked overnight in the dissolution medium, was tied to one end of opening was tied to the mouth of a PVC test tube (1cm diameter) and dipped in a 100 ml beaker containing STF (pH 7.4, 50 ml). The entire system was placed in beaker (250 ml)

containing distilled water maintained at 37±0.5 ◦C by used hot plate.

A small magnetic bead was placed in the beaker and was stirred at 100rpm on a magnetic stirrer (Remi India Ltd.). In-situ gel 1-ml volume, were withdrawn hourly intervals and replaced by an equal volume medium. The aliquots were diluted with the receptor medium and analyzed under UV spectrophotometry[14] .

ACCELERATED STABILITY STUDIES:

According to ICH guideline, the accelerated stability studies were carried for prepared in situ gelling systems. All the Formulations were analyzed for visual appearance, clarity, pH and drug remaining for 6 weeks of stability studies[15].

REFERENCES

1. Rathore KS. In-situ Gelling Ophthalmic Drug Delivery System: An Overview Int J Pharm Pharma Sci 2010; 2(4).
2. Mitali.Bodhankar M, Bhushan S, Bhoyar, Vinit V Agnihotri: Environmentally responsive ophthalmic gel formulation: based on combination with natural Polycationic copolymer Int. J. Pharm. Res. Dev.2012; 3(11):212-222.
3. Swati G, Suresh P Vyas: Carbopol/chitosan based pH triggered *in situ* gelling system for ocular delivery of Timolol Maleate. Sci. Pharm.2010;78:959-976.
4. Lalitkumar, Ravindra PS, Stuti G, Dhiraj K: *In situ* gel: a novel system for ocular drug delivery. Int. J. pharm. Sci. Rev. and Res.2011;9(2):83-91.
5. Bhoyar BS, Agnihotri VV, Bodhankar MM. New method for sustained ocular drug delivery: Based on Polymeric combination with Thermosensitive Gelling agents. Int. J. Res. Pharm. and Biomed. Sci.. 2011;2(3):1151-1160.
6. Jitendra, Sharma P.K. Banik A. and Dixit S. A New Trend: Ocular Drug Delivery System, Int. J.Pharm. July-2011Vol-2:3.
7. Nirmal H.B., Bakliwal S.R., Pawar S.P.," In-Situ gel: New trends in Controlled and Sustained Drug Delivery System";Int.J. PharmTech Res.2010,2(2).
8. Aparna V. Bhalerao, Singh Sitanshu S.. In situ gelling ophthalmic drug delivery system for glaucoma. International Journal Of Pharma And Bio Sciences.2,2, (2011),7-14.
9. Bhoyar B.S., Agnihotri VV. and Bodhankar M.M., 2011. New method for sustained ocular drug delivery: based on polymeric combination with thermo sensitive gelling agents. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2,3,1151-1160.
10. Katariya D. C., Poddar S.S.,2012. Current status of ophthalmic *in-situ* forming hydrogel. International journal of pharma and bio sciences. International journal Pharm Bio Science; 3,3, 372 – 388.
11. Asasutjarit.R., S. Thanasan., FuongfuchatA., VeeranS., 2011. Optimization and evaluation of thermoresponsive diclofenac sodium ophthalmic in situ gels. International Journal of Pharmaceutics. 411,128–135.
12. Jovita K., Sonker K, Pandey M, Kymonil K. M., Saraf S. A., 2012. Formulation and characterization of a novel pH-triggered in-situ gelling ocular system containing gatifloxacin. International Current Pharmaceutical Journal, 1,3, 43-49.
13. Peppas NA, Bures P., Leabandung W, Ichikawa H. Hydrogels in pharmaceutical formulations, Eur J Pharm and Biophar 2000;50:27-46.
14. Nagarwal R.C.,Kumar R.,Dhanawat M., Pandit J.K.,2011.Modified PLA nano in situ gel: A potential ophthalmic drug delivery system. Colloids and Surfaces B: Biointerfaces. 86, 28–34.
15. Suryawanshi Sarika S., Kunjwani H K, Kawade Jayashree V,Alkunte Mohita A, Yadav Dattatraya J. Novel Polymeric in Situ Gels for Ophthalmic Drug Delivery System. IJRPS 2012,2(1),67-83.