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Formulation and Evaluation of Ophthalmic in situ gel

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Abstract: The aim of this study was to develop In situ gel of Moxifloxacin Hcl. The poor bioavailability and therapeutic response of Conventional ophthalmic solutions due to short precorneal residence time and rapid elimination may be overcome by use of in situ gel forming system. It is instilled as eye drop and later on they undergo sol to gel transition in cul-de-sac. Hence in situ gel by ion sensitive method was prepared using gelling agent sodium alginate and the viscosity increasing agents like HPMC K100M,CMC Sodium and Xanthum gum to provide a sustained release . Suitable preservative like benzalkonium chloride was added. The in situ gels were further evaluated for clarity, pH, drug content, viscosity, gelation studies, sterility studies, Microbiological studies, In vitro diffusion studies, Ocular irritancy test. The results were highly agreeable showing in situ gels as an alternative in ophthalmic drug delivery showing improved bioavailability, increased precorneal residence time and providing sustained release upto 7 hours.

In situ gels should be easy to instill as eye drops and later on it gel in cul-de-sac forming in situ gel hence increasing contact time. The various approaches that are used in preparation of in situ gelling mechanism.

Various polymers like sodium alginate act as such ion activated gel. Gellan gum is another such polymer. They can be used alone or in combination with certain other viscosity increasing agents (HPMCK100M, CMC sodium, polyvinyl pyrrolidone, xanthum gum). Eyes have presence of calcium ions and Magnesium ions which help in gelling of Sodium alginate.

Keywords Moxifloxacin HCl, sodium alginate, Gelling solution ,in situ gel,, sustained release.(1)

Introduction:

Eyes are important sensory organs in the human body, which convert light to an electric signal that later will be interpreted by brain .It can restrict the entry of any exogenous substance because of its anatomical-physiological structure and defence mechanisms. But, as eyes are unique organs, they also can be infected by various diseases like conjunctivitis, dry eye syndrome, glaucoma, keratitis, trachoma and so on. Therefore, to target the drug at a required ocular site in therapeutic dose has been one of the most challenging tasks until now. Various factors like nasolacrimal drainage of drug, binding of drug to lachrymal protein, induced lachrymation, availability of limited corneal area create a barrier for absorption of drug through ocular routes.

There are two types of ophthalmic drug delivery systems, classified as conventional and newer drug delivery systems. The conventional ophthalmic drug delivery system in the form of eye drops, has a dynamic effect and high tear fluid turnover that causes rapid pre-corneal elimination of the drug and also only 1-10% of topically applied drug get absorbed that often results in poor bioavailability and therapeutic response. Consequently, to achieve the desired therapeutic effect, frequent instillation of concentrated solutions is needed. Due to tear drainage, more than 75% of the administered dose of the drug goes through the nasolacrimal duct and goes into the gastrointestinal tract, leading to systemic side effects. In order to enhance the ophthalmic bioavailability and lengthen the residence time of instilled dose, many ophthalmic vehicles have been developed, such as aqueous gels, inserts, ointments and suspensions.

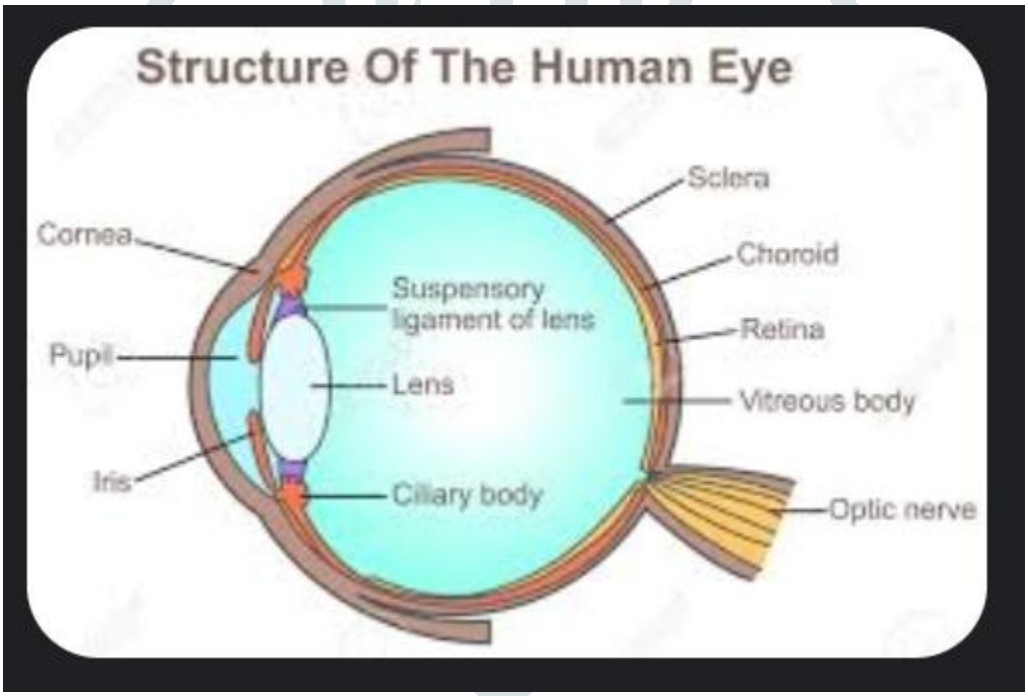
However, because of low patient compliance in using the inserts and the side effect of using an ointment such as blurred vision, these ocular drug delivery systems have not been used extensively until now.

In-situ gelling systems are described as low viscosity solution that phase transition in cul-de-sac to form viscoelastic gel. This sol-to-gel phase transition happens due to conformational changes of polymer in response to a physiological environment. In-situ formulations are more acceptable for patient because they are administered as solution or suspension which immediately undergoes to gelation as coming in contact with the eye.

Depending on the method chosen to cause sol-to-gel phase transition on the surface of the eyes, three types of in situ gelling systems are widely accepted namely ion activated systems, pH triggered systems and temperature sensitive systems. The ideal properties for in-situ gel formulation can be divided into three categories involving a physical state – the formulation should be free flowing liquid which allows ease of administration with reproducible dose delivery to the eyes:

Phase transition – as drug has been instilled, it should undergo sol-to-gel formation by phase transition.

Strength of gel – to withstand the shear force in cul-de-sac phase so it can prolong residence time of the drug, and the gel formed should be strong enough.(2)



Advantages:

1) Provide controlled and sustained release of the drug.
2) Ease of the drug administration.
3) Can be administered to unconscious patients.
4) Increased patient compliance and comfort.
5) Decrease the dose frequency and drug toxicity.
6) Increased bioavailability.
7) Provide biocompatibility and biodegradation due to use of natural polymers.

Disadvantages:

1) It requires high level of fluids.
2) The sol form of the drug is more susceptible for degradation.

3) Chances of stability problems due to chemical degradation.
4) Only drugs with small dose requirement can be given.
5) After placing the drug eating and drinking may become restricted up to the few hours.

Importance of in situ gelling system:

1) In-situ gel helps for the controlled and sustained release of the drugs by its "Sol-Gel" transition.
2) It helps in reducing frequency of drug administration in the body.
3) Low doses of the drugs are required and there will be no drug accumulation and side effects.
4) It increases bioavailability of drugs.
5) Residence time of drug will be increased due to gel formation.
6) The in-situ gel drug delivery system decreases wastage of the drug.(3)

Ideal characteristics:

1) It should be biocompatible.
2) It is capable of adhering to the mucus membrane.
3) Preferred pseudo plastic behavior of polymer.
4) Good tolerance and optical clarity is more preferred.
5) It should influence the tear behavior.
6) The polymer should be capable of decreasing the viscosity with increasing shear rate.(4)

Classification of In situ gel:

1) Based on physical stimuli
    a) Thermally Triggered System
    b) pH Triggered System

2) Based on physical mechanism
    a) Swelling
    b) Diffusion

3) Based on chemical reaction
    a) Ion cross linking
    b) Enzymatic cross linking
    c) Photo polymerization

In-Situ formation based on physiological stimuli:

a) Thermally Trigged System:
Temperature-sensitive hydrogels are possibly the most commonly studied class of environment-sensitive polymer systems in drug delivery research. The use of biochemical whose transitions from sol-gel is triggered by increase in temperature is a smart way to approach in-situ formation. In this system gelling of the solution is triggered by change in temperature thus satisfying 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. The ideal critical temperature range for such system is ambient and physiologic temperature such that clinical manipulation is facilitate 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 additions at the surface of skin or in the oral cavity. Three main strategies are occurs in engineering of thermo responsive sol-gel polymeric system. The temperature-sensitive hydrogels are classified into negatively thermo sensitive, positively thermo sensitive and thermally reversible Gels.Negative temperature-sensitive hydrogel have a Lower critical solution temperature (LCST) and contract upon heating below the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature is used for this resolve. One of the most extensively investigated polymers that exhibit useful LCST transition is poly (N-isopropyl acrylamide) (PNIPAAm). A positive temperature sensitive hydrogel has 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 (acryl amide-co-butyl methacrylate) have positive temperature required of swelling.

b) pH Triggered System:
Another formation of in situ gel based on physiologic stimuli ks formation of gel is made by pH changes. In this system gelling of the solution is triggered by a change in pH. At pH 4.4 the formulation is a free flowing solution which kndergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation pH4.4 into the tear film leads to an almost rapid transformation of the highly fluid latex into a viscous gel. All the pH-sensitive polymers contain dependent acidic or basic groups that accept or release protons in response to changes in environmental pH. The polymers with a great number of ionizable groups are Known as polyelectrolytes. Swelling of hydrogel increases as the exterior pH increases in 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 bioavailability and Partiality to be easily distant by tear fluid. To minimize this factors and exploit 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 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 solution 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 to attain gelation.

In Situ formation based on physical mechanism:

a) Swelling:
In situ gel formation material absorbs water from surrounding environment and expands to desired space. One such substance is myverol 18-99 (glycerol mono-oleate) which is polar 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.

b) Diffusion:
This method involves the diffusion of solvent from polymer solution into adjacent tissue and results in precipitation of polymer matrix. N methyl pyrrolidone (NMP) has been shown to be a suitable solvent for such system.

In Situ formation based on chemical reaction:

a) Ionic cross linking:
Polymers may undergo phase transition in existence of several ions. Some of the polysaccharides fall into the class of Ion-sensitive ones.20 While k-carrageenan forms rigid, fragile gels in account of small

amount of K+, i-carrageenan forms flexible gels mainly in the presence of Ca2+. Gellan gum economically available as Gelrite® is an anionic polysaccharide that goes through 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 that are Ca2+. Likewise alginic acid goes through gelation in presence of divalent/polyvalent cations. Example Ca2+ due to the contact with gluronic acid block in alginate chains.

b) Enzymatic cross linking:
In Situ formation catalysed by natural enzymes has not been considered widely but appears to have some advantages over chemical and photochemical approaches. For example, an enzymatic process works 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 which 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 appropriate mechanism for controlling the rate of gel formation which allows the mixtures to be injected before gel formation.

c) Photo polymerization:
Photo-polymerisation is commonly used for in situ formation of biomaterials. A solution of reactive macromer and initiator can be injected into a tissues site and the use of electromagnetic radiation to form gel. Acrylate or related polymerizable functional groups are normally used as the individual monomers and macromers because they rapidly undergo photo-polymerisation in the existence of suitable photo initiator. Typically long ultraviolet and visible wavelengths are used. Short wavelength ultraviolet is not used often because it has partial 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 while camphor quinone 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 for long term persistence in Vivo. Photo polymerizable systems when introduced to the desired site through injection get photo cured in situ with the help of fiber optic cables and then release the drug for prolonged period of time. The photo-reactions provide fast polymerization rates at physiological temperature. Furthermore, the systems are easily located in complex shaped volumes leading to an implant formation.(5)

Polymers used as In In-Situ Gelling agents are :

1) Gellan gum.
2) Alginic gum
3) Pectin
4) Carbopol
5) Chitosan
6) Xanthan gum
7) Xylogulan
8) Guar gum
9) HPMC

1) Gellan gum :

Gellan gum is an anionic hetero polysaccharide, secreted by microbe Sphingomonas elodea. It consists of glucose, rhamnose, glucuronic acid and linked together to obtained a tetrasaccharide unit.

Gelrite29 is deacetylated gellan gum, obtained by treating gellan gum with alkali to remove the acetyl group in the molecule. Due to instillation, gelrite forms gel because in presence of calcium ions. The gelation includes the formation of double helical junction zones followed by aggregation of double helical segment to form three dimensional networks30 by complexation with cations and hydrogen bonding with water. In food industry, gellan gum is used as suspending and stabilizing agent.

2) Carbopol:
Carbopol is a polyacrylic acid (PAA) polymer, which changed to gel as the pH is raised from 4.0 to 7.4. Carbopol remains in solution form at acidic pH but transform into a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol which enhance Viscosity of carbopol solution, while reducing the acidity of the solution. Comparing different types of poly (acrylic acid) (Carbopol 940-934-941and 910) 47 concluded that Carbopol 940 showed superior27 appearance and clarity.

3) Xylogulan:
Xyloglucan is also called as tamarind gum which is a polysaccharide obtained from the endosperm of the seed. Xylogulcan consists of three different oligomers like heptasaccharide, octasaccharide, nonsaccharide, which differ in number of galactose side chain. It is mainly used in oral, rectal, ocular drug delivery due to its non- toxic, biodegradable and biocompatible property. Like, poloxamer it exhibits gelation28 on heating refrigerator temperature or cooling from a higher temperature.

4) HPMC:
Cellulose is consists of glucan chain which has repeating B-(1, 4)-D-glucopyranose unit. Some natural polymers like HPMC, MC and EC these exhibit temperature sensitive sol-gel phase transition. Cellulose material will increases its viscosity when temperature is decreases while its derivatives like HPMC, MC, will also increase its viscosity when temperature is increased. MC is a natural polymer composed of native cellulose with alternate methyl substitution group on its chain. At low temperature (300C) solution is in liquid form and when temperature is increases (40-500C) and gelation36 occurred.

5) Alginic acid:

It is a linear block copolymer polysaccharide consists of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. In 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 diandtrivalent metal ions by a cooperative process involves consecutive glucuronic residues in the α-L glucuronic acid blocks of the alginate chain31.Alginic acid used as a vehicle for ophthalmic formulations, since it exhibits favorable biological properties such as biodegradable and non toxic.

6) Chitosan :

Gelling of chitosan occurs by two changes such as pH responsive change and temperature change. Chitosan is a natural component of shrimp and crab shell which consist of biodegradable, thermosensitive, poly cationic polymer obtained by alkaline deacetylation of chitin. Chitosan is a biocompatible pH dependent cationic polymer, which can 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 precipitation by the formation of a hydrated gel.(6)

Applicability of In- Situ polymeric drug delivery system:

Depending on the route of administration, these in situ polymeric systems may be classified as illustrated in following section –

a) Oral delivery
b) Ocular delivery
c) Nasal drug delivery system
d) Rectal and vaginal delivery
e) Injectable drug delivery system

a) Oral delivery:
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 main advantage of using pectin for these formulations is that it is water soluble, so organic solvents are not necessary in the formulation. In situ gelling gellan formulation as vehicle for oral delivery of theophylline is reported. The formulation consisted of gellan solution with calciium 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. An increased bioavailability with sustained drug release profile of theophylline in rats and rabbits was observed from Gellan formulations as compared to the commercial sustained release liquid dosage form.

b) Ocular delivery:
For in situ gels 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. Conventional delivery systems often result in poor bioavailability and therapeutic response because high tear fluids turn over and dynamics cause rapid elimination of the drug from the eye . So, to overcome bioavailability problems, ophthalmic in situ gels were developed much of the interest in the pharmaceutical application of gellan gum has concentrated on its application for ophthalmic drug deliver48. Drug release from these in situ gels is prolonged due to longer precorneal contact times of the viscous gels compared with conventional eye drops. Miyazaki et al. attempted to formulate in Situ gels for ocular delivery using Xyloglucan (1.5%w/w) as the natural polymer. These in situ forming polymeric systems were observed to show a significant mitotic response for a period of 4h when instilled into lower cul-de-sac of rabbit eye49. 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 with the water- soluble Carbopol system has been reported.

c) Nasal drug delivery system:
An in-situ gel system for nasal delivery of Mometasone furoate was developed and evaluated for Its efficacy for the treatment of allergic rhinitis. 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 sensitized rats was observed. In-situ gel was found to inhibit the Increase in nasal symptoms as compared to marketed formulation nasonex (mometasone furoate suspension0.05%). Intact ciliated respiratory epithelium and normal goblet cell appearance indicated from histopathology of rat nasal cavity proved that these formulations were safe for nasal administration.Wu et al. designed a new thermosensitive hydrogel by simply mixing N-[(2-hydroxy Methyltrimethyl ammonium)propyl]chitosan

chloride and poly (ethylene glycol) with a small amount of α-β-Glycerophosphate; for nasal delivery of insulin. The formulation was in solution form at room temperature that transformed to a gel form when kept at 37 degree.

d) Rectal and vaginal delivery:
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 thermoreversible 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. For a better therapeutic efficacy and patient compliance, mucoadhesive, thermosensitive, prolonged release vaginal gel incorporating clotrimazole-β-cyclodextrin complex was formulated for the treatment of vaginitis25. In addition, a significant reduction of drug C max was observed after administration of in situ polymeric system thus indicating the avoidance of adverse effects of indomethacin on nervous system.

e) Injectable drug delivery system:
The development of injectable in-situ forming drug delivery systems has received a considerable interest over the last decade. A novel, injectable, thermosensitive in situ gelling hydrogel was developed for tumor treatment. This hydrogel consisted of drug loaded chitosan solution neutralized with β-Glycerophosphate. Local delivery of paclitaxel from the formulation injected intra tumorally was investigated using EMT-6 tumors implanted subcutaneously on albino mice. Ito et al. designed and synthesized injectable hydrogels that are formed in situ by cross-linking of hydrazide modified hyaluronic acid with aldehyde modified versions of cellulose derivatives such as carboxymethylcellulose, hydroxypropyl methylcellulose and Methyl cellulose. These in situ forming gels were used for preventing postoperative peritoneal adhesions thus avoiding pelvic pain, bowel obstructions and infertility for a better therapeutic efficacy and patient compliance, mucoadhesive, thermosensitive, prolonged release vaginal gel incorporating Clotrimazole-β-cyclodextrin complex was formulated for the treatment of vaginitis.(7)

Evaluation of Ophthalmic in situ gel:

1) Clarity : The clarity of the formulations before and after gelling is often determined by visual examination of the formulations under light alternatively against white and black backgrounds . Additionally, the contents are often set in motion with a swirling action. Also, it is observed for the formation of turbidity or any unwanted particles dispersed within the solution.

2) pH : pH affects both the solubility and stability of the drug in the formulation. The formulation should remain stable at its pH and at the same time be non-irritating to the patient at the time of administration. The pH is measured by a digital pH meter. It should be pre-calibrated using standard buffers of pH 4 and pH 7 according to established procedures .

3) Gelling capacity: Gelling capacity is determined for in-situ gels for ophthalmic formulations. The in-situ gel is mixed with simulated tear fluid to examine the gelling ability of ophthalmic products. This is determined by visual observation of a drop of formulation during a vial containing 2.0 ml of freshly prepared simulated tear fluid. Gelation was visually assessed by recording the time and time it took for the formed gel to dissolve.

4) Gel – strength : This parameter can be evaluated using a rheometer. Depending on the gelation mechanism of the gelling agent used, a specific amount of gel is prepared from the form of the sol in the beaker. This gel, in the beaker, rises at a constant rate, so slowly push the probe into the gel. Changes in the load on the probe can be measured as a function of the probe

Immersion depth below the gel surface.

5) Gelation pH: Gelation pH is determined by an in-situ gel formation system incorporating a pH-sensitive polymer. The formulation is then placed in a beaker and 1M NaOH was added dropwise with continuous stirring. Use a pH meter (Equiptronics digital pH meter) to check the pH and while the viscosity is also measured. Changes in viscosity at each pH are recorded. The pH at which a rapid change in viscosity is observed is referred to as gelation pH .(8)

Conclusion :

Moxifloxacin hydrochloride, a broad spectrum antibacterial agent used in the treatment of ocular infections, was successfully formulated as in situ gel-forming eye drops using Sodium alginate as a gelling agent in combination with HPMC as a viscosity enhancing agent. Thus, the developed formulation is a viable alternative to conventional eye drops by virtue of its ability to enhance bioavailability through its longer precorneal residence time and ability to sustain drug release. Also important is the ease of administration afforded and decreased frequency of administration resulting in better patient acceptance.(9)

References:

1) Nitan Bharti Gupta,et.al, International Journal of Pharmaceutical Research and Applications, Volume 6.
2) Kurniawansyah I S, et al, pH Triggered In-situ Gelling Ophthalmic Drug Delivery System, International Journal of Drug Delivery Technology 2018.
3) Mayuri R. Khule, et.al , A Review: in-situ Gel Drug Delivery System, International Journal of All Research Education and Scientific Methods (IJARESM), Volume 9, Issue 3, March -2021.
4) Ramanjit Saini,et.al, In Situ Gels- A new trends in Ophthalmic drug delivery system , International Journal of Pharma Sciences and Research (IJPSR), Vol 6 No 05 May 2015.
5) Garge Lajri, et.al , Ophthalmic pH Sensitive In-Situ Gel: A Review, Journal of Drug Delivery and Therapeutics, ISSN: 2250-1177.
6) Dibyalochan Mohanty, et.al , A Review on in situ Gel: A Novel Drug Delivery System, Int. J. Pharm. Sci. Rev. Res., 50(1), May – June 2018; Article No. 25, Pages: 175-181.
7) Nirmal H.B, et.al, In-Situ gel: New trends in Controlled and Sustained Drug Delivery System, International Journal of Pharm Tech Research CODEN (USA): IJPRIF ISSN : 0974-4304 Vol.2, No.2, pp 1398-1408, April-June 2010.
8) TUSHAR R. PANDHARE, A Review on Concept of In Situ Gel andIts Applications, International journal of pharmacy and pharmaceutical research, November 2020 Vol.:19, Issue:4.
9) Sonjoy Mandal,et.al, Formulation and evaluation of an in situ gel-forming ophthalmic formulation of moxifloxacin hydrochloride, September 28, 2016.