International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

Ophthalmic in Situ Gel: A Review

Vrushabh S. Yeole, S. D. Pande*, Shubham G. Wagh,
Samiksha D. More, Shruti A. Adhau,
Department of Pharmaceutics, Vidhyabharti College of Pharmacy, Amravati- 444602

Submitted: 15-05-2022 Revised: 20-05-2022 Accepted: 25-05-2022

ABSTRACT: Eye is the most complex and sensitive organ of the body. Ocular drug delivery is challenging field because of complicated anatomical structure, small absorptive surface, short precorneal time. Less than 10% of the administered drug enters the eye. The conventional ocular drug delivery system has drawback such as loss of drug due to tears, blinking, obscured vision, non-sustained action. All these consequences ultimately lead to poor ocular therapy. To overcome the issues with conventional ophthalmic dosage form in situ ophthalmic gels are prepared. This system can help in sustained release of the drug at the site of action due to its special characteristics of sol – gel transition. In situ gel forming systems are drug delivery systems that are in solution form at the time of administration and then convert to gel form once administered. When exposed to physiological conditions (e.g., pH, temperature, and ionic concentration), in situ gelling systems quickly undergo a sol-gel phase transition into a viscoelastic gel. This review is to specify basic anatomy and physiology of eye, variousmethods for in situ gelling systems. Also, their mechanismsof gel formation, types of smart polymers and evaluation of polymeric in situ gel.

Key words:Polymers, IN- situ gel, Sol-gel transition, Smart polymers, PH-sensitive, Ion-sensitive.

I. INTRODUCTION:

The majority of ophthalmic medications are given topically in the form of eye drops, which are a dosage form made up of a buffered, isotonic aqueous solution or drug suspensions. A standard dropper filled with traditional ophthalmic solution produces approximately 50-70µl per drop, with a portion of these drops immediately draining until the eye returns to its typical resident volume of 7µl. Because of the drug loss in front of the eye, only a little amount of drug can reach the cornea and inner tissue of the eye Traditional ocular delivery techniques such as eye drops have low bioavailability and therapeutic responsiveness due to high tear fluid turnover and dynamics, which cause fast precorneal drug loss. A high frequency of eye drop instillation iscorrelated with patient non-compliance.Including excess amount of drug in a formulation to solve a bioavailability problem can be harmful if the drug solution drained from the eye is absorbed systemically through the nasolacrimal duct.in ophthalmic drug delivery, a challenging task is normal ocular protective processes likeblinking,tears drainage; that promote rapidclearance, reduce bioavailability which results short duration of pharmaceutical response.[1]

Toenhance corneal residence time and increase bioavailability, different ophthalmic delivery systems like gels, suspension, collagen shield and inserts are developed. These formulations havenot been extensively accepted due to impaired vision, unpredictability in dose administered, adhering of eye lids, and patient discomfort. In situ gel-forming solutions, which are infused as drops into the eye and undergo a sol-gel transition in the cul-de-sac, can be used to solve these problems.[2]

The ‘in situ gel’ system has emerged as one of the novel drug delivery systems, the in-situ gelling system helps for the sustained and controlled release of the drugs, improved patient complianceby its unique characteristic feature of ‘Sol to Gel ‘conversion an in-situ gelling system is a formulation that is in solution form before entering the body, but changes to gel form under different physiological conditions. Temperature, pH change, solvent exchange, UV radiation, and the presence of certain molecules or ions all influence the sol to gel transition. Drug delivery systems with the above-mentioned ‘sol to gel transition' features can be widely exploited for the production of long-term delivery vehicles for bioactive compounds. The manufacture of in situ gels can be done with both natural and synthetic polymers. As a result, in situ ophthalmic gels are preferable to traditional ocular dosing forms.[3]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

II. ANATOMY AND PHYSIOLOGY OF EYE :

Although small in size, the eyes are one of the most complicated organs in the human body. They act alike to a video camera, and transfer the images you see to the brain for processing and storing. The cornea, a transparent, thick layer that protects the eye's surface, allows light to enter the eye. The light rays then pass through the pupil (the black circle in the center of the eye) and the lens. As light travels through the pupil, the iris muscle causes the pupil's diameter to alter in size as the light changes.When there is too much light, the pupil shrinks to prevent light rays from entering. When there is insufficient light, the pupil expands, or dilates, to allow more light rays to enter. The lens is located behind the pupil and is responsible for focusing the images that are perceived by the eye. [4,5]

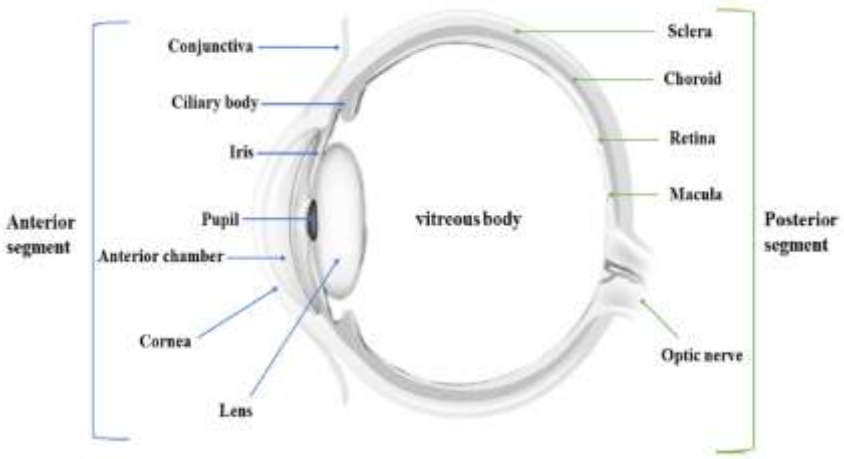


Fig. 1 – The anatomy of ocular system: the anterior segment involves conjunctiva, ciliary body, pupil, anterior chamber cornea and lens; the posterior segment consists of sclera, choroid, retina macula and optic nerve.[6]

III. PHYSIOLOGICAL CONSIDERATIONS:

Physiological restrictions significantly restrict the amount of an ophthalmic medication that can be absorbed. The relatively impermeable corneal barrier is one of the factors that limit ocular absorption. The epithelium, endothelium, and inner stroma are the three main absorptive barriers that make up the cornea. Ion transfer is blocked by the epithelium facing tears, which has lipophilic cellular layers. The corneal epithelium's tight connections act as a selective barrier for tiny molecules, preventing macromolecules from diffusing via the paracellular pathway.

The stroma, which makes about 90% of the cornea, is a very hydrophilic layer beneath the epithelium. Maintaining proper corneal hydration is the job of the corneal endothelium. The more lipophilic the medications are, the more resistance they will encounter when crossing the stroma. The epithelium becomes more resistant to drugs that are more hydrophilic, however stroma and endothelium resistance is limited. The route and rate of penetration through the corneal membrane in the cul-de-sac are affected by physicochemical drug qualities such as lipophilicity, solubility, molecular size and shape, charge, and degree of ionisation.[7]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

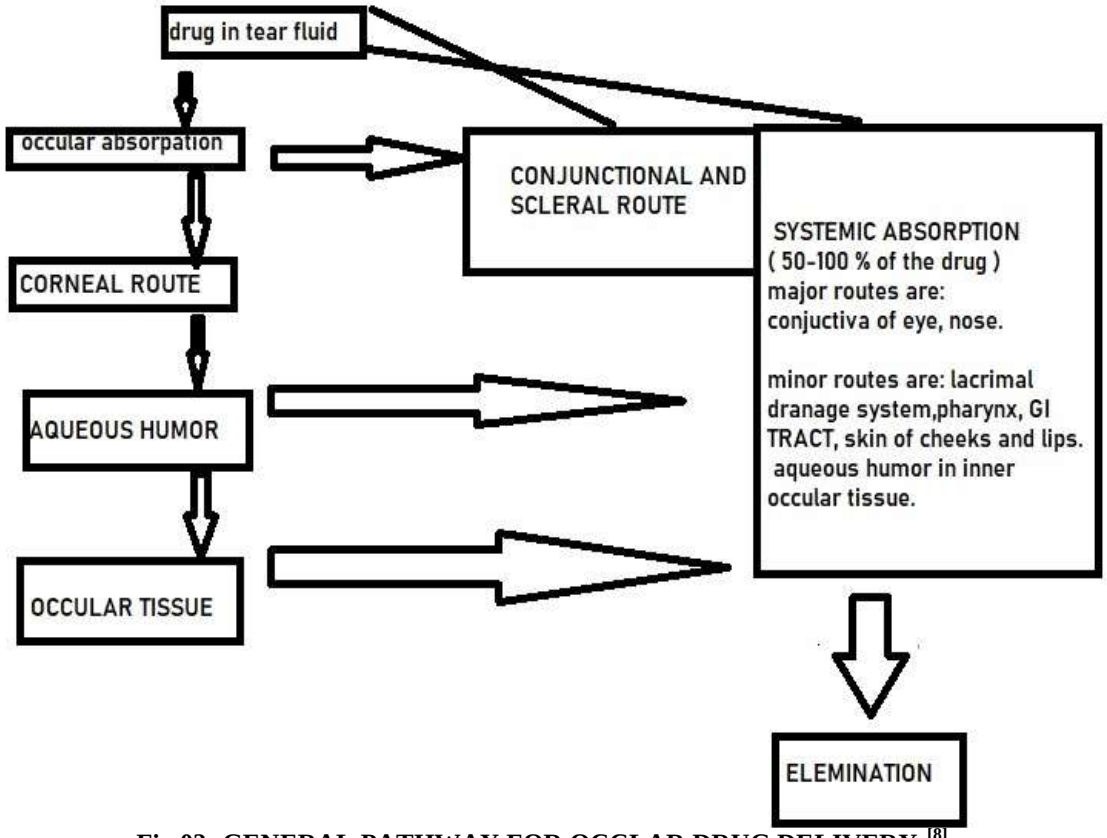


Fig.02: GENERAL PATHWAY FOR OCCLAR DRUG DELIVERY:[8]

Challenges in ophthalmic drug delivery system:

The special issue of creating a therapeutic system is achieving an adequate drug concentration at the active site for the right period in order to give high therapeutic efficacy for ocular delivery systems. Drug absorption is hampered by the cornea's architecture, physiology, and barrier function. Maintaining a therapeutic medication level in the tear film or at the site of action necessitates frequent instillations of eye drops. However, using extremely concentrated solutions on a regular basis may cause toxic side effects and cellular damage at the eye surface. The major challenges to anterior segment drug delivery following topical administration include solution drainage, lacrimation, tear dynamics, tear dilution, tear turnover, conjunctival absorption, nonproductive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane. Because of these physiological and anatomical limitations, only a small portion of the medication is absorbed by the eyes, roughly 1% or less of the implanted dose. Topical formulations must have a balance of lipophilicity and hydrophilicity, as well as a longer contact period, in order to be clinically efficacious.[9]

IV. OCCULAR DRUG ABSORBTION:

Mechanism of ocular drug absorption: Instillation drugs must reach the eye and do so primarily through the cornea, then through non-corneal pathways. Drug diffusion over the conjunctiva and sclera is involved in these non-corneal pathways, which appear to be particularly relevant for drug that are poorly absorbed by the cornea.[10]

Corneal permeation:cornea is outer most and sensitive layer of eye.it acts as a mechanical barrierand prevent the entry of exogenous substance thus have a protective function. In terms of trans corneal drugpermeation, the cornea can be considered to consist of three primary layers (epithelium, stroma and endothelium). It is the primary route for ocular absorption. Lipophilic drugs can easily by through this route to reach at ocular tissue. local administration of conventional drugs via the corneal route fails to provide adequate concentrations within the vitreous and retina due to

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

large molecular size of drug as molecular size of drug decreases penetration is enhanced.[11]

Non-corneal permeation: non corneal permeation occurs mainly through conjunctional and scleral route. Hydrophilic drug can pass easily through this route. the conjunctiva is outer layerand composed of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers substantially less resistance to topical administered drug.Conjunctive contributes to formation of tear film. Sclera is more permeable than conjunctiva and cornea. It is made up of collagen and mucopeptide which allow diffusion of drug to posterior segment such as retina, choroid, vitreous humor etc. [12]

V. OCULAR PHARMACOKINETICS :

The drug pharmacokinetics from the eye follows the following paths. [13,14]

a. Trans corneal permeation from the lacrimal fluid into the anterior chamber.
b. Non-corneal drug penetration into the anterior uvea through the conjunctiva and sclera.
c. Drug distribution from the blood stream and into the anterior chamber. Topical administered drug crosses the cornea and enter the aqueous humor, followed distribution to ocular tissues such as choroid, retina.
d. Elimination mainly occurs through nasocramialduct. Some drug is eliminated by systemic pathway.
e. Elimination of drug from aqueous humor by its turnover through the chamber angle and sclemm's canal.
f. Drug elimination from the vitreous via posterior route across the blood-retina barrier.
g. Drug elimination from the vitreous via anterior route to the posterior chamber.

VI. MECHANISM OF DRUG RELEASE INTO THE EYE :

- **Diffusion:** The medicine is continually released at a predetermined pace via the membrane into the tear fluid through the diffusion mechanism. Drug release can be controlled by slow disintegration of solid distributed drug within this matrix due to inward diffusion of aqueous solution. When the insert is inserted into the eye, tear fluid begins to infiltrate the matrix, causing swelling, polymer chain relaxation, and drug diffusion.
- **Osmosis:** in the osmosis mechanism, the insert comprises a transverse impermeable elastic membranedividing the interior of the insert into a first compartment and a second compartment. The first compartment is bounded by a semi-permeable elastic membrane. Second compartment is bounded by an impermeable material and the elastic membrane. There is a drug release aperture in the impermeable wall of insert. The first compartment contains a solute which cannot pass through the semi-permeable membrane and the second compartment provides a reservoir for drug which is in liquid or gel form. When the insert is placed in aqueous environment of the eye, water diffuses into the first compartment and stretches the elastic membrane toexpand the first compartment and contact the second compartment so that drug is forced through the drug release aperture.[15]
- **Bioerosion:**When the ocular insert comes into touch with tear fluid, the matrix is eroded, allowing the drug to be released in a continuous manner. The drug is available as a dispersed in the ocular insert, but it is thought that if it is present in a superficial concentrated matrix form, the drug will release in a more controlled manner. [16]

APPROACHES TO IMPROVE OCULAR DRUG DELIVERY: -

- Viscosity enhancer
- Gel (hydrogel and organogel)
- Prodrug or double prodrug
- Eye ointment
- Liposomes
- Niosomes
- Penetration enhancer
- nanosuspension
- Microemulsion
- nanosphere
- implants
- in situ- forming gel

VII. IN SITU GELLING SYSTEM:

In the early 1980s, a new concept of creating a gel in situ (e.g., in the cul-de-sac of the eye) was proposed for the first time. it is well acknowledged that raising the viscosity of a medication formulation in the precorneal region increases bioavailability by causing the cornea to drain more slowly. several in situ gelling system concepts have been researched. when the environment [ph, temperature, ion] changes, in situ gels are changed to gel form. the physical or chemical crosslinking of polymer chains causes

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

gelation. polymers that are biodegradable and water soluble can be employed. in order to create an in situ ophthalmic gel, smart polymers are used.[17]

ADVANTAGES:followingare the advantages of in situ gelling system.[18]

a) Easy administration like a conventional eye drop formulation,
b) Ease of fabrication,
c) Patient compliance,
d) Sustained and controlled drug release due to formation of gel network,
e) Enhancement of drug bioavailability, and
f) Prolonged retentivity at the site of action
g) reduced frequency of applications hence improved patient compliance and comfort.
h) Generally, more comfortable than insoluble or soluble insertion.
i) Less blurred vision as compared to ointments.

Generally defined mechanism uses for triggering the in-situ gel:

A. Physiological mechanism
B. chemical reaction

Diffusion: -In-situ gel formulation uses diffusion as a type of physical technique. In this procedure, the solvent from the polymer solution diffuses into the surrounding tissue, causing the polymer matrix to precipitate or solidify. In the development of in-situ gelling systems, N methyl pyrrolidone (NMP) has been a popular polymer.[19]

Swelling: - in-situ formulation uses a type of physical method called swelling. the polymers surrounding the polymer ingest and the fluids existing in the outer environment swell from outside to inside in this technique, allowing the medicine to slowly release. myerol (glycerol mono-oleate) is a polar lipid that expands in the presence of water to produce lyotropic liquid crystalline phase structures. this material possesses bioadhesive characteristics and can be degraded in vivo by enzymes. [20]

BASE ON CHEMICAL REACTION:

- Ionic cross linking
- Photopolymerization
- Enzymatic cross-linking

Enzymatic cross-linking:- formation of gel take place by crosslinking with enzymes present in body fluid. Most suitable method because gel formation is controlled by enzymes. More advantages and reliable than chemical and photo chemical method. [21]

Ionic-crosslinking: ion sensitive polymer under goes phase transition and get converted to gel, in the presence of ions like Na^+,K^+,Ca^+,Mg+. tears consist of all these ions which help to form gel. [22]

TYPE OF INSITU GEL:

1. Thermo-sensitive in situ gels
2. pH sensitive in situ gels
3. Ion sensitive in situ gel

VIII. APROACHES FOR IN SITU GELLING SYSTEM:

1. **pH triggered in situ gelling polymers:** all pH sensitive polymers have a pendant acidic or basic group that accepts or releases protons in response to Ph changes. Polyelectrolytes are polymers with a large number of ionizable groups. Hydrogel swelling increases when the polymer has a weakly acidic group, but decreases when the polymer contains a weakly basic group. For example, (PAA), (PEG), and Carbopol. [23-25]

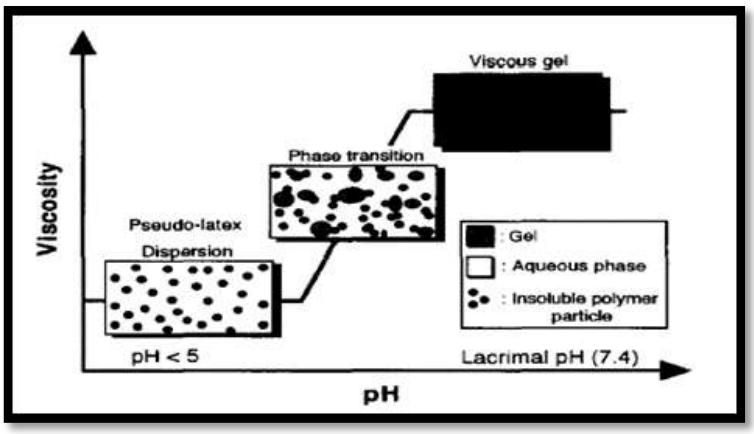


Fig -03: Schematic of mechanism Ph triggered in situ gelling systems [32]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

2. **Ion triggered in situ gelling system:**When exposed to an ionic concentration of tear fluids, the solution viscosity in an ion induced in situ gelling system increases. Osmotically induced gelation is another name for i**t**. Ion sensitive polymerase able to crosslink with cations (monovalent, divalent) present in lacrimal fluid on ocular surface and increase ocular the retention time of drug. The electrolyte of tear fluids such as Na^{+}, $Ca2^{+}$, Mg2+. Are suited for the initiate gelation. Ex. Gellan gum, sodium alginate, pectin. [26-28]

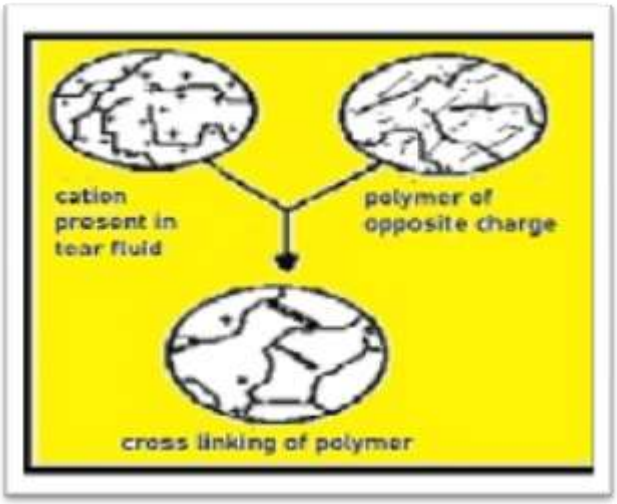


Fig-04: Schematic of mechanism of ion triggered in situ gelling systems [32]

3. **Temperature-sensitive gelling system:** temperature-sensitive in situ gelling systems are arguably the most researched type of stimuli-sensitive polymer systems. Temperature changes serve as an external stimulation for these systems. The lower critical solution temperature is the temperature at which the sol-gel transition occurs (LCST). The fundamental reason for sol to gel conversion is thought to be a variation in solubility at different temperatures. Hydrogen interaction between the hydrophilic groups on the polymeric surface and the water molecule supports greater dissolution of the polymer chains at temperatures below the LCST, and the system remains in the form of a solution. The hydrogen bonds in the system deteriorate when the temperature rises over LCST. As a result, the hydrophobic interaction increases, making sol-gel transformation easier. [29-31]

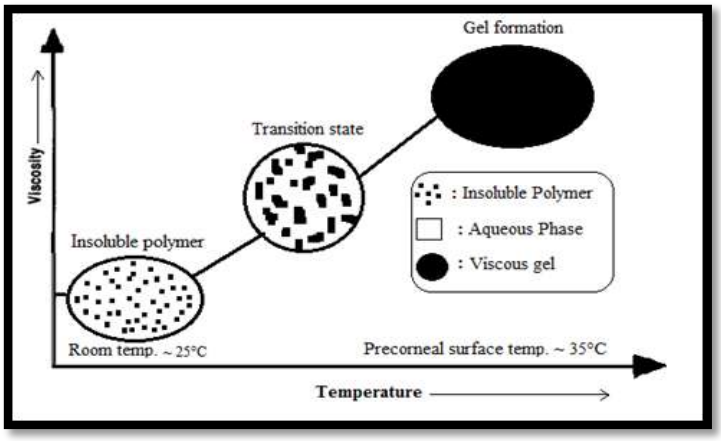


Fig-05: Schematic of temperature triggered in situ gelling system [32]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

IX. POLYMERS:

Polymer, any of a class of natural or synthetic substances composed of very large molecules, called macromolecules, that are multiples of simpler chemical units called Monomers.Polymers are obtained from natural sources as well as chemically synthesized. They are classified as biodegradable and non-biodegradable. Polymers, which govern the release of a drug from the formulation, are the backbone of a pharmaceutical drug delivery system. Biodegradable polymers are more acceptable in use since they can be reduced to harmless monomers, and a biodegradable polymer control release mechanism can provide a steady rate of drug release. Natural polymers can be employed as a platform to achieve predetermined medication delivery rates and physio-chemical features with ease of availability while serving as a polymer or drug delivery system. [33,34]

A. IDEAL CHARESTRICTICS OF POLYMERS:

Polymer to be used in in situ gel should have following properties.[35]

1] It should be biocompatible
2]It should have pseudo plastic behavior
3]It should have good optical activity.
4]It should influence the tear behavior.
5]It should not harm or irritate eye.

B. **POLYMERS USED IN FORMULATION OF IN SITU GEL:**

Polymers example, and their characteristics are given in below table. [36-37]

POLYMER	ORIGIN	CHAREGE	**S**OLUBILITY IN WATER
Carbomer	synthetic	anionic	soluble
chitosan	natural	cationic	soluble
Xanthan gum	natural	cationic	insoluble
poloxamer	synthetic	nonionic	soluble
HPMC	natural	nonionic	soluble
Sodium alginate	natural	anionic	soluble
Gallan gum	natural	anionic	soluble
xyloglucan	natural	nonionic	soluble
Sodium alginate	natural	anionic	soluble

X. POLYMER USED IN PH SENSITIVE IN SITU GELLING SYSTEM:

[A]**CARBOPOL:**Carbopol polymers are acrylic acid-based polymers with a high molecular weight and crosslinking. These are acrylic acid polymers that have been crosslinked using polyalkenyl ethers or divinyl glycol. They're made from primary polymer particles with an average diameter of 0.2 to 6.0 microns. Carbopol polymers are frequently used in a range of pharmaceutical dosage systems, including controlled release tablets, oral suspensions, and other Novel Delivery Systems, as well as topical applications like ocular in situ gel. [38]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

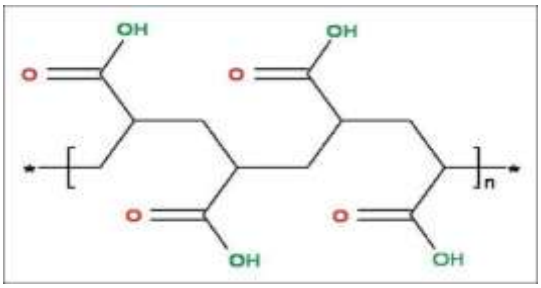


Fig- 06: chemical structure of carbopol

Physical and chemical properties: Carbopol polymers have excellent water sorption properties. When exposed to a pH environment above 4.0 to 6.0, they expand in water up to 1000 times their original volume and 10 times their original diameter, forming a gel. Because these polymers have a pKa of 6.0 to 0.5, the carboxylate moiety on the polymer backbone ionizes, causing repulsion between the native charges, which causes the polymer to swell. In powder form, Carbopol polymers have a glass transition temperature of 105°. When the polymer comes into contact with water, however, the glass transition temperature drops dramatically. This causes the polymer (221°F) to swell.

Mechanism: When a molecule of one of these polymers is dispersed in water, it begins to hydrate and uncoil somewhat, increasing viscosity. However, in order to get the best results from the polymer, the molecule must be entirely uncoiled. The molecule can become completely uncoiled in two ways, providing maximum thickening and bio adhesion performance. The most typical approach is to neutralize the polymer with an appropriate base. The Carbopol polymer is ionized during neutralization, resulting in negative ions along the polymer backbone. The molecule entirely uncoils due to repulsions between like negative charges, and gelling begins. This is a quick reaction that leads in efficient performance. This is simple to accomplish with (sodium or potassium hydroxide or amine bases). Only amines should be used to neutralize less polar or non-polar solvent solutions.[39]

A hydroxyl donor is used in a second thickening method. Because hydrogen bonds are formed when a carboxyl group and one or more hydroxyl donors are combined, thickening occurs. This technique is time-dependent, and maximum thickening might take anywhere from five minutes to several hours. As a result, the pH of such systems will be acidic.[40]

Uses:

1. Gelling agent,
2. stabilizing,
3. thickening agent,
4. suspending agent.

Carbopol	Molecular weight	viscosity
910	4,000,000	3000-7000
940	3000,000	40000-60,000
934	3000,000	30,000- 40,000
941	1,2500	29000-39,400

TYPES OF CARBOPOL:

[B]**CHITOSAN**:chitosan is a copolymer consisting of N-acetyl-2-amino-2-deoxy-d-glucopyranose and 2-amino-2-deoxy-d-glucopyranose, where the two types of repeating units are linked by (1→4) -- glycosidic bonds. chitosan is a naturally occurring polymer, cationic in nature and soluble in water. Uses as drug carrier in pharmaceutical preparation.[41]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

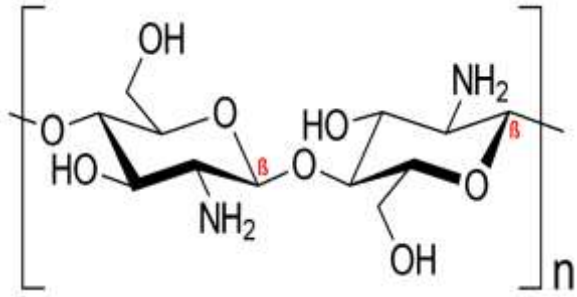


Fig-07: Chemical structure of chitosan

Properties: Chitosan gelling is caused by two factors: a change in pH responsiveness and a change in temperature. Chitosan is a biodegradable, thermosensitive, polycationic polymer produced by alkaline deacetylation of chitin, which is found naturally in shrimp and crab shells. Chitosan is a biocompatible cationic polymer with a pH of 6.2 that may stay dissolved in aqueous solutions. The production of a hydrated gel occurs when a chitosan aqueous solution is neutralized to a pH greater than 6.2. [42]

Mechanism: Due to acidic or basic groups in the polymer structure, pH-responsive gels vary their physical and chemical properties at different pH values. Basic groups are protonated at acidic pH, while acidic groups are deprotonated in alkaline media. Chitosan exhibits a sol–gel transition at pH 6.5 when the medium shifts from slightly acidic to neutral, due to its cationic character. Chitosan is deionized and forms a three-dimensional network when pH rises. As a result, chitosan gels swell to an acidic pH as amino groups are protonated, causing repulsions between polymeric chains. Due to the ionization of acidic groups, anionic gels based on carboxymethyl chitosan swell in basic media. pH-Responsive Ocular in Situ Gels Based on Chitosan Due to acidic or basic groups in the polymer structure, pH-responsive gels change their physical and chemical properties at different pH levels.

USES:

1. suspending agent
2. thickening agent

XI. POLYMER USED IN TEMPATURE SENSITIVE IN SITU GELLING SYSTEM:

[A]**Hpmc:**HPMC (hydroxy propyl methyl cellulose) is a partly o-methylated and o-(2-hydroxyl propylated) cellulose, obtained by treating alkali cellulose with chloromethane and propylene oxide.

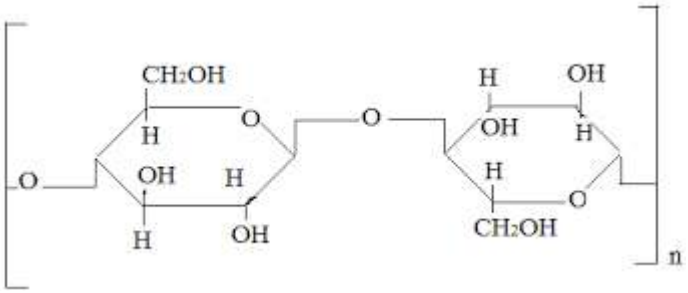


Fig 08: Chemical structure of HPMC

Properties:t's an odorless and tasteless creamy white or white granular or fibrous powder. In cold water, HPMC can be dissolved. To make aqueous dispersions, the material is dispersed in about 25% hot water (80 °C) with rapid agitation. An adequate amount of cold water is added and mixed once the HPMC has been properly hydrated. HPMC dispersions have a gel point of 50 to 90 degrees Celsius. HPMC is a viscoelastic, non-ionic hydrophilic semi-synthetic polymer that is commonly used as a lubricant in controlled release dosage forms for ophthalmic therapies. HPMC has a pH-independent medicine release profile. [47]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

Mechanism:HPMC macromolecules are hydrated at low temperatures, and there is little polymer-polymer interaction other than simple entanglement. The polymers gradually lose their water of hydration as the temperature rises, which is represented in a decrease in relative viscosity. When the polymer dehydrates sufficiently but not completely, polymer–polymer connections form, and the system approaches an infinite network structure, as evidenced by a dramatic increase in relative viscosity. In situ gelling systems have been created using this sol–gel transition. At 23 °C, these systems had low viscosity and produced soft gels at 37 °C.[48]

GRADES OF HPMC: -

hpmc grades	viscosity (cps)	released mechanism
HPMC K100LV	100	erosion
HPMC K4M	4000	Swelling / difussion
HPMC E4M	3000-5,600	Swelling / difussion
HPMC K15M	15000	Swelling / difussion
HPMC K100M	100,000	Swelling / difussion

USES:
1. suspending agent;
2. coating agent
3. viscosity increasing agent.
4. Controlled release agent

[B]**POLOXAMER:**Poloxamers are also known by their trade name Pluronics".Poloxamers are nonionic triblock copolymers comprised of a central hydrophobic chain of polyoxypropyleneand two hydrophilic chains of polyoxyethylene present on alternate side.[49]

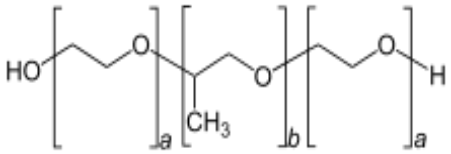


FIG -09chemical structure of pluronic

Properties: The temperature-dependent self-assembling and thermo-gelling behavior of poloxamer solutions is an essential feature. In a reversible process, concentrated aqueous solutions of poloxamers are liquid at low temperatures and gel at higher temperatures. The polymer composition influences the transitions that occur in these systems. Several molecular weights are available, each with a particular gelling behavior, depending on the ratio and distribution of hydrophilic and hydrophobic chains. It has a high-water solubility.[50]

Mechanism: The gelation process is reversible, and the temperature at which it occurs is known as the sol-gel transition temperature. Poloxamer solutions remain fluid below Tsol-gel, but above this temperature, the solution solidifies into a semi-solid substance. The hydrophobic interactions between the poloxamer 407 copolymer chains cause the thermal gelation. The poloxamer 407 copolymer chains begin to combine into a micellar structure as the temperature rises. The dehydration of the hydrophobic PPO repeatsunit's resultsin the creation of micelle structures, which is the first stage in the gelation process. Tsol-gel is concentration-dependent, increasing as the concentration of poloxamer 407 in aqueous solution is reduced until a lower level is achieved, at which time poloxamer 407 no longer gels. Tsol-gel can also be increased or decreased by adding active pharmaceutical substances, salts, excipients, and other chemicals to poloxamer 407-based formulations. [51]

POLAXMER TYPES:

polaxmer	molecular weight	physical form	trade name
124	2200	liquid	pluronic l44
188	8400	solid	pluronic f68

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

407	12600	solid	pluronic l121
338	14600	solid	pluronic f108
237	7959	solid	pluronic f87

USES:
1. Thickening agent,
2. binding agent,
3. emulsifying agent.

[c] XYLOGLUCAN: -Xyloglucan is the principal hemicellulose of primary cell walls of dicots and in about half of the monocots. It is structurally related to cellulose as it shares the same backbone of ß (1 .4)-linked glucose residues. The main repeating unit contains four glucose units. Three out of four glucose units are substituted with a (1 .6) xylose residues. Some xylose units are further substituted by galactose through a ß (1 .2) bond. In addition to these sugar units, the galactose residues can be further substituted with a (1 .2) fucose. [52]

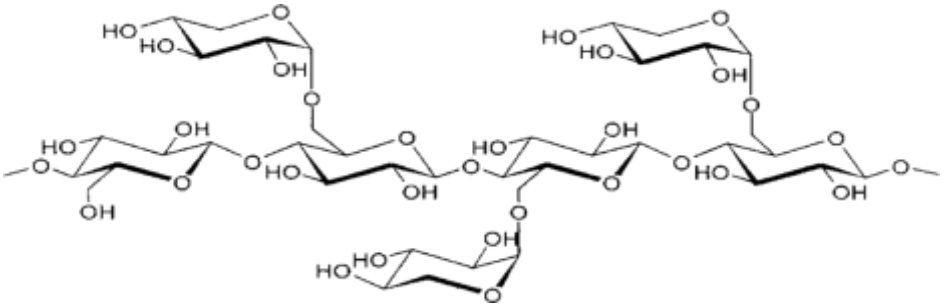


Fig – 10: Chemical structure of xyloglucan

Properties: - The XG side chains give raise to radically different physical properties of the polymer compared to cellulose; xyloglucan is highly water soluble and cannot form ordered crystalline microfibrils as cellulose.
Mechanism: - Xyloglucan, a polysaccharide derived from tamarind seed, forms thermoresponsive gels in water, under certain conditions. Xyloglucan is composed of a (1-4)-ß-Dglucan backbone chain (GLU) which presents (1-6)-a-D-xylose branches (XYL) partially substituted by (1-2)-ß-D-galactoxylose (GAL). The transition temperature is inversely related to polymer concentration and the galactose removal ratio. For example, the sol–gel transition of xyloglucan was shown to decrease from 40 to 5 °C when the galactose removal ratio increased from 35 to 58%. [53]

uses:
1. thickening agent
2. binding agent

XII. POLYMER USED IN ION-SENSITIVE IN SITU GELLING SYSTEM:

[A]**GALLEN GUM:** Gellan gum (GG), biodegradable and non-toxic in nature. It is anionic polysaccharide.

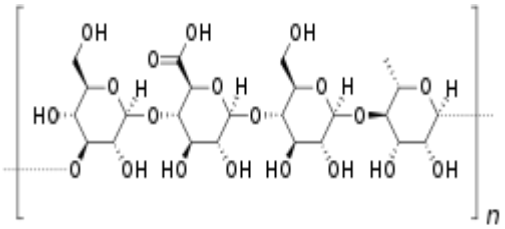


fig-11: chemical structure of gallan gum.

Properties: Gellan gum has ability to bear heat and acid stress during fabrication. It is thermoresponsive biocompatible, biodegradable. The beads of GG swell at high pH and are stable at low Ph. Being negatively charged polysaccharide.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

Mechanism:GG exhibits gelling properties. It can make hard, transparent gels that are stable at low pH levels. During gelation, the strength, presence, and type of cations, pH, temperature, and polymer concentration all play a role. In the presence of metallic ions, GG forms a transparent gel that is temperature and acidic media resistant. Gelling of gellan gum may be achieved by enzymatic linkages, by adding salt, by treating with heat and by applying pressure. GG has characteristic to produce strong gel at low concentrations.Gellan gum may create gels containing any ion, such as sodium, calcium, and magnesium. In the presence of multivalent ions such as Ca+2, Zn+2, Pb+2, Al+3, and others, it exhibits inotropic gelation. [55,56]

Types of Gallen gum:

TRADE NAME	COMMAN NAME
Gelrite™	acyl gellan gum
Kelcogel™	deacylated gellan gum

USES:
1. Thickening agent
2. Binding agent.
3. Stabilizers
4. Gelling agents

[B] **Alginates:** -unbranched binary copolymers, alginates consist of (1 .4) linked ß-D-mannuronic acid (M) and a-Lguluronic acid (G) residues of widely varying composition and sequence. By partial acid hydrolysis, alginate was separated into three fractions. Two of these contained almost homopolymeric molecules of G and M, respectively, while a third fraction consisted of nearly equal proportions of both monomers and was shown to contain a large number of MG dimer residues

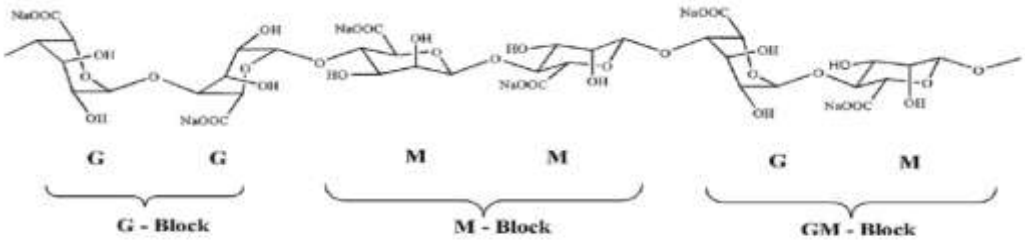
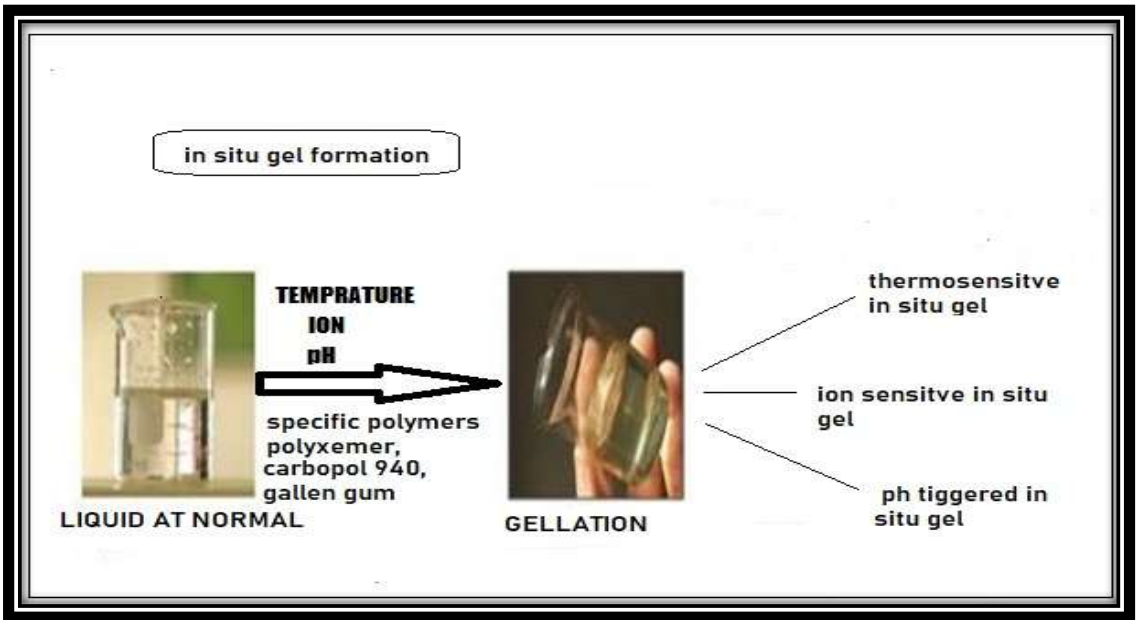


fig -12: Chemical structure of alginates.

Properties:Alginate is a naturally occurring anionic polymer derived from brown seaweed that has been extensively studied and used for a variety of biomedical applications due to its biocompatibility, low toxicity, low cost, and moderate gelation when divalent cations such as Ca2+ are added.[57]
Mechanism: -The alginate forms 3-dimensional ionotropic hydrogel matrices, generally by the preferential interaction of calcium ions with the G moieties resulting in the formation of inhomogeneous gel. Calcium-crosslinked alginate gels have shown good mechanical properties even when prepared from relatively low solution concentrations of the polymer, ~0.5% w/v, and they can physically entrap a whole array of molecules, and sustain their release.[58]
Uses:- 1]suspending agent
2] Gelling agent

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

DIAGRAMATIC REPRESENATION OF FORMULATION OF IN SITU OPHTHALMIC GEL:



XIII. EVALUATION PARAMETERS FOR IN SITU OPTHALMIC GEL :

PH: In ocular formulations, pH impacts both solubility and stability of formulation. It should be designed in such a way that the formulation remains stable at that pH while also causing no irritation to the patient when administered. It is determined using digital pH meter. [59]

Evaluation of Isotonicity: Isotonicity is an important property of ophthalmic preparations. To avoid tissue damage or eye discomfort, isotonicity must be maintained. Isotonicity testing is performed on all ocular preparations that have good release properties, gelling capability, and the required viscosity. The formulation is blended with a few drops of blood and compared to a typical commercial ophthalmic preparation under a microscope at 45x magnification.

Rheological Parameter: The viscosity measurements can be calculated by using Brookfield viscometer, cone and plate viscometer. The in-situ gel formulation was placed in sampler tube. The formulation before gelling should have viscosity from 5 to 1000 mpas. After ion gel activation in the eyes, it will have viscosity of about 50-50,000 mpas. The samples are analyzed both at room temperature at 25°c and thermo stated at 37°c ± 0.5°c by a circulating bath connected to viscometer adaptor prior to each measurement.

Ocular Irritancy Test: The Draize irritancy test was created to determine the ophthalmic product's ocular irritation potential prior to marketing. The amount of substance given to the eyes is generally 100l inserted into the lower culde-sac with observation of the various criteria made at a defined required time interval of 1 hr, 24hrs, 48hrs, 72hrs, and 1 week following administration, according to the Draize test. The investigation included three male rabbits weighing 1.5 to 2 kg. The sterile formulation is administered twice daily for seven days, followed by a cross-over study (a three-day washing phase with saline was performed before to the cross-over study). Rabbits are checked for redness, swelling, and watering on a regular basis. [60]

Accelerated Stability Studies: Formulations are placed in ambient-colored vials and sealed with aluminum foil for a short-term accelerated stability study at 402°C and 755% RH, as per International Conference on Harmonization (ICH) recommendations. The clarity, pH, gelling capacity, medication content, rheological evaluation, and in vitro dissolution of samples are all tested once a month.[61]

Gelling capacity: By dropping a drop of a freshly prepared formulation into a vial containing 2 ml of stimulated tear fluid (STF) and recording the time it takes for the 'gel' to form or dissolve in 7.4 pH phosphate buffer, the time can be used to determine the appropriate polymer concentrations or gelling agent for in situ gelling systems.

2nd Technique: -

They utilized water-soluble dye such amaranth, Congo red, indigo blue, and others, which they

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

blended with the created in situ gel after dissolving 1 g in distilled water. The gelling capabilities of the formulations were determined in vitro by inserting 5 ml of gelation solution (STF) in a glass test tube and keeping the temperature at 370.5 °C. It turned into a rigid gel-like substance almost instantly.

The existence of the gel's stiffness is used to assess its gelling capacity in vitro. And the length of time that the gel was thickened remains constant. The colour was also added to the gel to give it a visual appeal. The gelling capacity period was computed based on the three categories in vitro.

+'gel' forms after a few minutes and disperses quickly

++gelation occurs instantly and lasts for a few hours

+++ Gelation happens almost instantly and lasts for a long time.

In vitro drug release study: The Franz diffusion cell was used to conduct an in vitro drug release analysis of an in-situ gel solution. In the donor compartment, the formulation is inserted, and in the receptor compartment, newly made stimulated tear fluid is placed. A dialysis membrane is placed between the donor and the receptor. The entire assembly is then placed in a magnetic stirrer that is thermostatically controlled. The medium's temperature was kept at 37°C +0.5°C. At a predetermined time, interval of 1 hr. to 6 hrs, 1 ml of sample is extracted and replaced with the same volume of fresh. The withdrawn sample is diluted to 10 mL in a volumetric flask with the appropriate solvent and analyzed using blank reagent in a UV spectrophotometer at the appropriate wavelength. The drug content is determined by applying an equation derived from a standard calibration curve. The cumulative drug release percentage is calculated.

sol-gel transition temperature and gelling time: - this evaluation test is performed on thermosensitive polymer-based compositions. The sample is stored in a tube for these tests, which is kept at a set temperature and subsequently heated at a specific rate. When no movement of the sample is visible after the test tube is tilted, the gel is said to be formed. Gelling time can be defined as the time it takes to detect gelation for the first time, as described above. [62]

Texture analysis: The texture profile analyzer is used to evaluate the consistency, stiffness, and cohesiveness of in situ gel. This largely refers to the gel's strength and ease of use. Texture analysis offers information on hardness, compressibility, and adhesiveness, which can be connected with criteria such as ease of removal from the container, good spread ability on the corneal surface, and adherence to the mucous layer to extend residence time.

Sterilization using autoclaving: For 20 minutes, all test tubes containing formulation should autoclaved at 121C, 15 Psi. Furthermore, utilizing previous autoclaved samples, in-vitro physiochemical characteristics such as percent labelled quantity, flow ability, pH, viscosity, and sol-gel transition temperature were analyzed to see if there were any changes in the physiochemical parameters due autoclaving. [63]

XIV. CONCLUSION:

Use of water soluble and biodegradable polymers makes the in situ ophthalmic gel more acceptable because minimum chances of irritation. In situ ophthalmic gel has benefit over the conventional dosage form such as stability, biocompatibility, formulation remain in contact with eye surface for longer period of time, and patient compliance. All this makes the in situ ophthalmic gel more preferrable for the treatment of eye.

REFERANCES:

[1]. Eaga Chandra Mohan, Jagan Mohan KandukuriPreparation and Evaluation of In-Situ-Gels for Ocular Drug Delivery: Journal of Pharmacy Research 2009; vol 2(6),1089-1094.

[2]. Tinu T S, Litha Thomas1, Anil Kumar B: Int. J. Pharm. Sci. Rev2013;**vol**30, page 176-183.

[3]. Wadhwa Karan*, Sharma Chandan: a novel approach towards ocular drug delivery:European Journal of Biomedical and Pharmaceutical Sciences 2018;vol 5(6); page 237-244.

[4]. Lee Ann Remington **(ed.)**: Clinical Anatomy and Physiology of Visual System, 7th; 2020: page 1-137.

[5]. Wiley Black Well (ed.): Clinical Anatomy of the Eye, 2nd; 2013: page 1-200.

[6]. Yumeiwu, Yuanjuan Liu: Research progress in in situ gelling ophthalmic gelling system. Asian Journal of Pharmaceutical Sciences 2019; **vol** 14: page 1-15.

[7]. Kishore Cholkar, SupriyaRedddy: Eye anatomy, physiology and barrier to drug deliverypublished by Wood Head Publishing Limited 2013: page 1-15.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 508-524 www.ijprajournal.com ISSN: 2456-4494

[8]. Sachin Pathak and Himansu Chopra: current trends for ophthalmic drug delivery: a review: International Journal of Pharmacy and Biological Science 2014: vol4(2): page 163-173.
[9]. Patel PB, Shastri DH, Shelat PK, Shukla AK; Ophthalmic Drug Delivery System: Challenges and Approaches; Systematic Reviews in Pharmacy;2010; vol 1(2); page no: 113-120.
[10]. Sridhar MS: Anatomy of cornea and ocular surface: Indian Journal of Ophthalmology 2018; **vol** 6: page 190-194.
[11]. RamaiyanDhanapal, J. Vijaya Ratna:ocular drug delivery system: a rewiveinternational journal of innovative drug discovery2012;**Vol** 2(1): page4-15.
[12]. DeeptaGhate& Henry F Edelhauser Expert Ocular absorption following topical delivery,Drug Deliv. (2006) 3(2): page275-28
[13]. P. Tangri, S. Khurana: Basics of Ocular Drug Delivery Systems: international Journal of Research in Pharmaceutical and Biomedical Sciences 2011; **Vol**. 2(4); page 1541-1550.
[14]. Agrahari,V., Mandal, A., and Mitra, A. K., :"A comprehensive insight on ocular pharmacokinetics," Drug Deliv. Transl. Res., 6(6), pp. 735–754, 2016.
[15]. M. k.sikandar, p. k. sharma and s. visht: ocular drug delivery system: an overview: international journal of pharmaceutical sciences and research; 2011; vol. 2(**5**):page 1168-1175.
[16]. Amandeep Singh, Deepa Negi: Recent trends in ocular drug delivery: journal of pharma asppiere 2018: vol 10(2). Page 55-67.
[17]. Gupta, A., Formulation and Evaluationof In Situ Ophthalmic Drug Delivery System. International Journal of Pharmaceutical & Biological Archive, 2012; vol 3(4). Page 715-718.
[18]. Agarwal, K., In-situ gel formation for ocular drug delivery system an overview. Asian Journal of Biomedical and Pharmaceutical Sciences, 2011; 1(4). Page 15-19
[19]. KristiinaJtirvinena, Tomi J&vinenb,: The Advantages of In situ Gel from Every Different FormulationInternational Journal of Research in Pharmaceutical SciencesDecember 2020 : 11(4):7198-7206
[20]. Patil, R.N.and R.S.Kumar, In situ gelling system: novel approach for ophthalmic drug delivery: WorldJournal of Pharmacy and pharmaceutical science, 2014; vol 3(7): 423-440.
[21]. Sneha Vaidya, AporavLaxmikantDeulkar: Formulation development and evaluation of long acting ophthalmic in situ gelling system of dorzolamide hydrochloride 2013; International Journal Drug Development and Research 2013. Vol 5(4): page 156-163.
[22]. Asmat Majeed and Nisar Ahmed Khan; Ocular in situ gel and overview. Journal of Drug Delivery and Therapeutics 2019; vol 9(1): page 337-347.
[23]. Suresh Chand, Diksha Sharma: Formulation and evaluation of pH sensitive in situ ocular gel. International Journal of Pharmaceutics and Research 2018; vol 08(02): page 19028-19035.
[24]. Jayant Deshpande: Design and development of pH monitored in situ gel of lomefloxacin. Journal of Pharmaceutical Science and Bioscientific Research 2013; vol 3(1): page 10-13.
[25]. Ophthalmic pH Sensitive In-Situ Gel: A ReviewGargeLajri and SaudagarRavindranath Journal of Drug Delivery & Therapeutics. 2019; 9(2-s): page 682-689.
[26]. Jain D, Kumar V, Singh S, Mullertz A, Bar-Shalom D. Newer trends in in Situ gelling systems for controlled ocular drug delivery:J Anal Pharm Res. 2016; 2(3): 00022.
[27]. San sunakkurniawansyaa, taofik,rusdian:in situ ophthalmic with ion activated system. International journal of applied pharmaceutics 2019; Vol 11(4); page 15-18.
[28]. C.Vijaya, K Shweta goud: Ion-activated In Situ Gelling Ophthalmic Delivery Systems of Azithromycin 2011; ind journal of pharmaceutical science; 73(6);615-620.
[29]. Geethalakshimi, Venkates: Temperature triggered in situ ophthalmic system for betaxolol in glaucoma. Journal of Applied Pharmaceutics 2013: vol 3(02): page 153-159.
[30]. Padmajwaklar: Thermosensitive in situ gel for ocular delivery of lomefloxacin. Indian journal of Pharma, edu and Research 2015: vol 50(2): page 96-101.
[31]. Development and in vitro/in vivo evaluation of thermo-sensitive in situ

gelling systems for ocular allergy mayMerve Güven1, Murat Sami Berkman. Braz. J. Pharm. Sci. 2019; page 55.
[32]. Jain D, Kumar V, Singh S, Mullertz A, Bar-Shalom D. Newer trends in in Situ gelling systems for controlled ocular drug delivery:J Anal Pharm Res. 2016; 2(3): 00022.
[33]. Pawar Dipali Sanjay, Patrekar Prasad Vasantrao: Polymers Used in Pharmaceuticals: A Brief Review; international Journal of Pharma and Chemical Research 2016; vol 4(2) page235-238.
[34]. M. MADAN*, A. BAJAJ, S. LEWIS1, N. UDUPA1 AND J. A. BAIG. In Situ Forming Polymeric Drug Delivery SystemsIndian J. Pharm. Sci., 2009, 71 (3): 242-251
[35]. Krushnakumar J Gandhi*, Subhash V Deshmane,polymers in pharmaceutical drug delivery system: a review: international journal of pharmaceutical sciences review and research 2012; vol 14(2) page 56-65.
[36]. Snehalnikode, gauri dixit and kanchanupadhya: in situ gel: application and uses of polymers: world journal of pharmacy and pharmaceutical sciences 2016; vol5(7) page 1638-1658.
[37]. takayukiyoshida, tszchunglai: ph- and ion-sensitive polymers for drug delivery: expert opin. drug deliv ,2013: vol11(10): page1-17.
[38]. anamica and p.p. pande: An Overview on Smart pH Responsive Polymers 2018; vol 30(4); page 711-713.
[39]. Prabhakarpanzade and prshantk.puranik: Carbopol polymer: a versatile polymer for pharmaceutical application.:journal of pharmaceutical and technology2010;3(3): page 12-15
[40]. Fenny indahsafitri, desynawangsari: application of Carbopol 940 in gel. Journal of health science and research2021; vol34; page 120.
[41]. Roberta cassano: gel based material for ophthalmic delivery:journal of gels 2020;vol 7(3) ; page 130
[42]. M.Dash,f.Chiellini: chitosan – a verssitile semi synthetic polymer in bio medical application: journal of polymer science 2011;vol 36; page981-1014.
[43]. Teodora Irimia: Chitosan based in situ gel for ocular delivery. Journal of Marine Drugs 2018; vol 16: page 370.
[44]. Munwar a. Mohammed, syeda, k.m. Wasan.: an overview of chitosan and its application in non-parenteral delivery system:journal of pharmaceuetical science 2017; vol 9 ; page 53.
[45]. Anuja t. Kadam, rahul . Jadhav: design and evaluation of modified chitosan based in situ gel for ocular drug delivery2017; international journal of pharmacy and pharmaceutical sciences; vol 9(11); page 87-91.
[46]. R. M. Gilhotra, D. N. Mishra: Alginate-chitosan film for ocular drug delivery: Effect of surface cross-linking on film properties and characterization, Pharmazie (2008) vol 63: 576–579
[47]. Goparoybiswas: hpmc; different aspect indrug delivery: journal of pharmacy and pharmacology 2017; vol 4; page 381-385.
[48]. Wu Huichao, Du Shouying: The application of biomedical polymer material hydroxy propyl methyl cellulose (HPMC) in pharmaceutical preparations: Journal of Chemical and Pharmaceutical Research, 2014, 6(5):155-160.
[49]. Karim A.Soliman K Ullah, A Shah: Poloxamer-based in situ gelling thermoresponsive systems for ocular drug delivery applications: Drug Discovery Today2019,vol 5 page 036.
[50]. Z.m.a.Fathalla, a. Vangala, m. Longman, k.a. Khaled, a.k. Hussein, o.h. El-garhy, r.g.Alany,poloxamer-based thermoresponsive ketorolac tromethamine in situ gel preparations: design, characterisation, toxicity and transcorneal permeation studies:, european journal of pharmaceutics and biopharmaceutics (2017), vol 1; page 1-30
[51]. Payam Zarrintaja, ZahedAhmadib: Poloxamer-based stimuli-responsive biomaterials: Materials Today: Proceedings 2018; vol 5; page 15516–15523.
[52]. S Miyazaki 1, S Suzuki, N Kawasaki,: In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride , int journal of pharmaceutics; 2001 Oct 23;229(1-2):29-36.
[53]. Ahmed, V.A.; Goli, D. Xyloglucan based in-situ gel: formulation development and evaluation of in-situ ophthalmic gel of brimonidine tartarate. Indo Global J. Pharm. Sci., 2018; 8(3): 92-103.

[54]. Ankit Acharya, Prakash Gounadanavar: Preparation of gellangum and chitosal based in situ gel of timolol meleat. Acta Scientific Pharmaceutical Science 2018: vol 3(2): page 68-78.
[55]. Khalid Mahmood Zia, ShaziaTabasum, Muhammad Faris Khan, Nadia Akram, Naheed Akhter, Aqdas Noreen, Mohammad Zuber, Recent trends on Gellan Gum blends with natural and synthetic polymers: A review,:International Journal of Biological Macromolecule 2017; vol 109; page 1068-1087.
[56]. Kuen Yong Leea,b, David J. Mooney, : Alginate: Properties and biomedical applications Progress in Polymer Science 37 (2012) 106–126.
[57]. R. M. Gilhotra, D. N. Mishra: Alginate-chitosan film for ocular drug delivery: Effect of surface cross-linking on film properties and characterization, Pharmazie (2008) vol 63: 576–579.
[58]. Sarada K, Firoz S, Padmini K: In-Situ Gelling System: A Review: International Journal of Current Pharmaceutical Review and Research 2014-15, vol 5(4): page 76-90.
[59]. Rathore KS. In situ gelling ophthalmic drug delivery system: an overview. Int J Pharm Sci Res. 2010; 2:30-34.
[60]. Patel HA, Patel JK, Patel KN et al. Ophthalmic drug delivery system- a review. Sch Res Lib. 2010; 2:100-115.
[61]. Patil AP, Tagalpallewar AA, Rasve GM et al. A novel ophthalmic drug delivery system: in situ gel. Int J Pharm Sci Res. 2012; 3: 2938- 2946.
[62]. Meshram S, Thorat S. Ocular in Situ gels: Development, evaluation and advancements. Sch Acad J Pharm. 2015; 4(7): 340- 346.
[63]. Balu A, Johnson T, Sundara R, Seetharaman S: Optimization and Evaluation of Temperature Triggered in situ Gel Formulation using Design of Experiments (DoE) and HET-CAM Test. J Nanomed. 2020; 3(1): 1031.