IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
May 2023 Vol.:27, Issue:2

A Review on *In-Situ* Gelling System for Sustained Ophthalmic Release

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Panchamy Nair K[*1], Prasobh G R[2], Varsha V R[3], Vishnupriya B V[1], Shabin P[1]

*[*1] BPharm, Sree Krishna college of pharmacy and research center Parassala, Thiruvananthapuram, Kerala, India.*

[1] B Pharm, Sree Krishna college of pharmacy and research center Parassala, Thiruvananthapuram, Kerala, India.

[2] Principal, Sree Krishna college of pharmacy and research center Parassala, Thiruvananthapuram, Kerala, India.

[3] Assistant professor, Department of pharmaceutics, Sree Krishna college of pharmacy and research center Parassala, Thiruvananthapuram, Kerala, India.

Submitted: 20 April 2023
Accepted: 26 April 2023
Published: 30 May 2023

Keywords: *In situ* gel, Approaches, Polymers, Properties, Methods, Evaluation, Advancement

ABSTRACT

In situ gel have become one of the prominent and accessible novel drug delivery system. It helps for sustained and controlled release of drug by special characteristic feature of sol to gel form. Here in ophthalmic administration liquid on instillation undergo phase transition in cul-de-sac form viscos - elastic gel under physiological condition such as temperature modulation, pH change, presence of ion and UV light. Both natural and synthetic biodegradable polymer used in formulation of polymer. In situ gel are evaluated for this physical strength, appearance and performance in in vitro in vivo studies. Recent development in field of polymer science allow use to *in situ* gel in different drug delivery system like ocular, nasal, rectal, vaginal etc. This study focuses on *in situ* gel in ophthalmic release, its various approaches, polymers, method of preparation and application. In this review, deals with introduction, advantage and disadvantages, mechanism, approaches, polymers, method of preparation, evaluation and recent advancement.

INTRODUCTION

Vision impairment and blindness are the most global concern health problem which result in social and economic burden. Drug delivery to the interior/posterior segment in the ocular system face challenges because of their protective barrier and elimination mechanism. The conventional method of drug delivery result in less than 5% ocular bioavailability. Over the past few years, different type of novel approaches is developed for improving drug delivery. But safety, simple, and effective drug delivery was major concern. Among ophthalmic drug delivery in situ gelling system attain great attention [1].

In situ gelling system has the great potential in the wide areas of drug delivery. It can be formulated not only as gels but also as nanosphere, microsphere and liposomes. To overcome all the drawback of conventional drug delivery a newer concept of insitu gelling system was came into light in early 1980s.In situ gel are liquid during instillation into eye and undergo rapid gelation form viscoelastic gel and slowly release the drug. This system enhances the bioavailability of systemic absorption of drug by the increase the residence time and sustained release of the drug. In situ gel formation can be achieved either by changing in temperature, pH, and ion activated system [1].

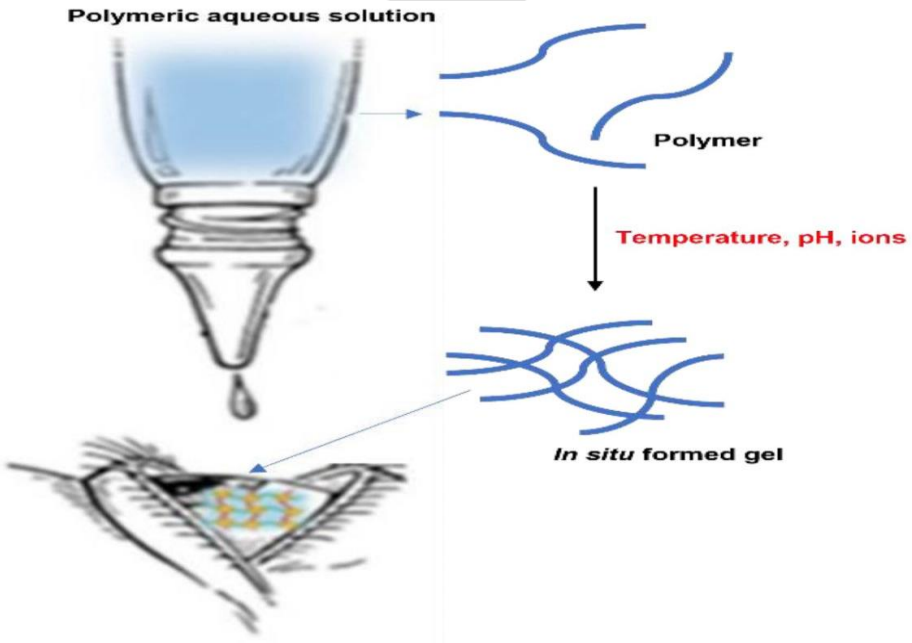

Figure.1: Formation of in situ gel

ANATOMY OF EYE

Eye is a complex organ with unique anatomy and physiology. In physiological point of view, eye can be divided into 2 main segments: anterior and posterior segment. Anterior segment occupies one third while posterior segment occupied remaining. Tissue such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Cornea forms the outermost layer of the eye. It is found directly on the front side of the iris and pupil; it is an avascular and transparent part of eye. The conjunctiva, a thin and clear membrane, cover front surface of the eye and the inner surface of the eyelids. It consists of goblet cell and non-keratinized epithelium cell. Its main function is to protect the eyes from microbes. Conjunctiva cover 17 times the surface that is covered by cornea and drug permeation more from conjunctiva than from cornea. Aqueous humor is clear watery fluid inside the front of eye. It is nontransparent which allow the light to get through it. They provide nutrition and maintain the eyes normal shape and pressure [2].

Posterior segment includes sclera, choroid, retinal pigment epithelium, optic nerve and vitreous humor. As per anatomical point of view eyeball consist of a transparent shell comprises of 3 layers – the outer coat, tunica media, the intima. The sclera is made up of highly resistant tissue extending to the front of the eye forming transparent tissue, the cornea. The drug which is hydrophilic in nature generally penetrate through sclera without any hinderance as compared to cornea and conjunctiva this is due to the presence of proteoglycans in between the collagen mess which is aqueous in nature. The function of sclera includes its serve as protective layer of the eye and maintains intraocular pressure. The middle layer is mainly composed of cribriform tissue, richly vascular and pigmented and divided into 3 – iris in front, choroid at back ciliary body in between them. Retina is highly differentiated nerve membrane behind the visual receptor [2].

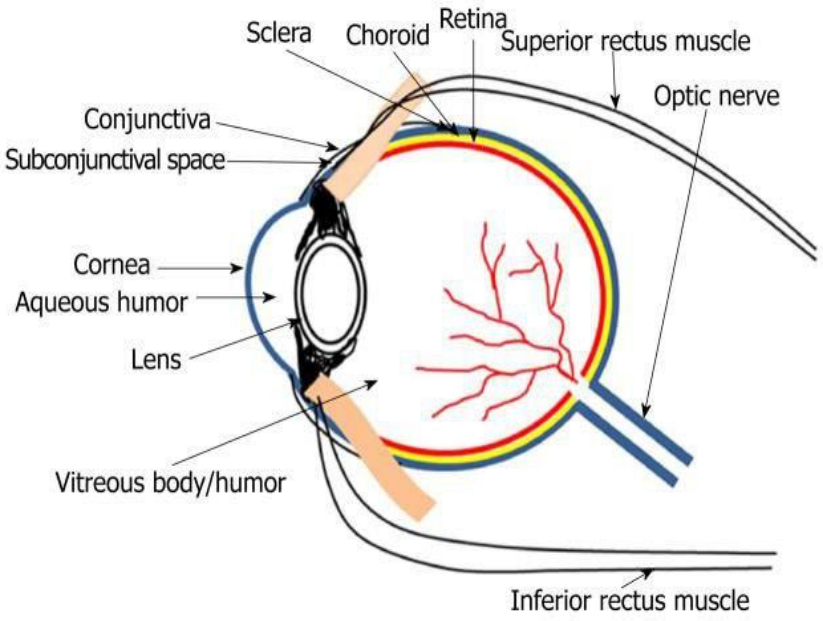

Figure. 2: Structure of eye

ADVANTAGES OF INSITU GEL [3]

- Ease of drug administration.
- Sustained and prolonged drug release.
- Minimize the dose frequency and drug toxicity.
- Increased bioavailability.
- It can be administered to unconscious patient.

DISADVANTAGES OF IN SITU GEL [3]

- Sol form of drug is more susceptible for degradation.
- Stability problem occur due to chemical degradation.
- Only drug with small dose can be given.
- Lower mechanical strength result in premature dissolution or flow away of gel from targeted local site.

MECHANISM OF INSITU GEL

In situ gel system formation is done by two mechanism such as physical and chemical mechanism.

PHYSICAL MECHANISM

Physical mechanism consists of the following:

- **DIFFUSION**

In this method involve diffusion of solvent from polymer solution into surrounding tissue result in solidification or precipitation of polymer matrix.

- **SWELLING**

In this method the polymer is surrounding the polymer imbibe and the fluids that are present in exterior environment which swell from out to inside and drug release slowly [4].

CHEMICAL MECHANISM

Chemical reaction result in situ gelation involves following processes:

- **ENZYMATIC CROSS LINKING**

In this method gel is formed by crosslinking with the enzyme which are present in body fluid. In this enzymatic process handles efficiency under physiological condition and no need for possibly destructive chemicals such as monomer and initiators.

- **PHOTO-POLYMERIZATION**

In this photo polymerisation method electromagnetic radiation are used formation of in situ gelling system. A solution of reactive monomers and invader can be injected into a tissues site and the application of electromagnetic radiation used to form gel.

- **IONIC CROSS LINKING**

In this method the ion sensitive polymer is used, which undergo phase transition in presence of ions like Na^{+}, Ca^{2+}, $K^{+}$and Mg^{2+}[4].

VARIOUS APPROACHES OF INSITU GEL

Various approaches of insitu gelation system are,

1. TEMPERATURE TRIGGERED INSITU GELLING SYSTEM

Temperature is the most widely used stimulus in environmentally responsive polymer system in in situ gelling formulation. In this system, thermos responsive or temperature responsive polymers are used that show a drastic and discontinuous change in their physical properties with temperature. These polymers show a miscibility gap at high or low temperature and an upper or lower critical solution temperature exists. Thermal induced or thermal sensitive in situ gel classified into 3 types:

- Negative thermosensitive type
- Positive thermosensitive type
- Thermally reversible type[4]

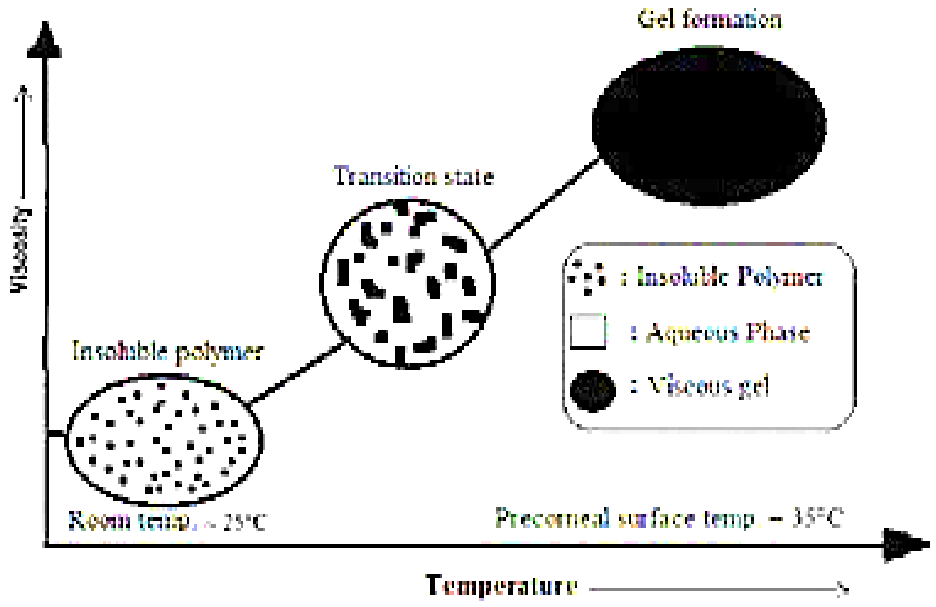

Figure.3: Scheme of temperature triggered in situ gel

2. PH TRIGERRED IN SITU GELLING SYSTEM

In this approach, pH responsive or pH sensitive polymer to be used to form a gel. All pH sensitive polymer contains acidic or alkaline ionizable functional groups and that either loose or let accept protons in comeback to change in pH [4].

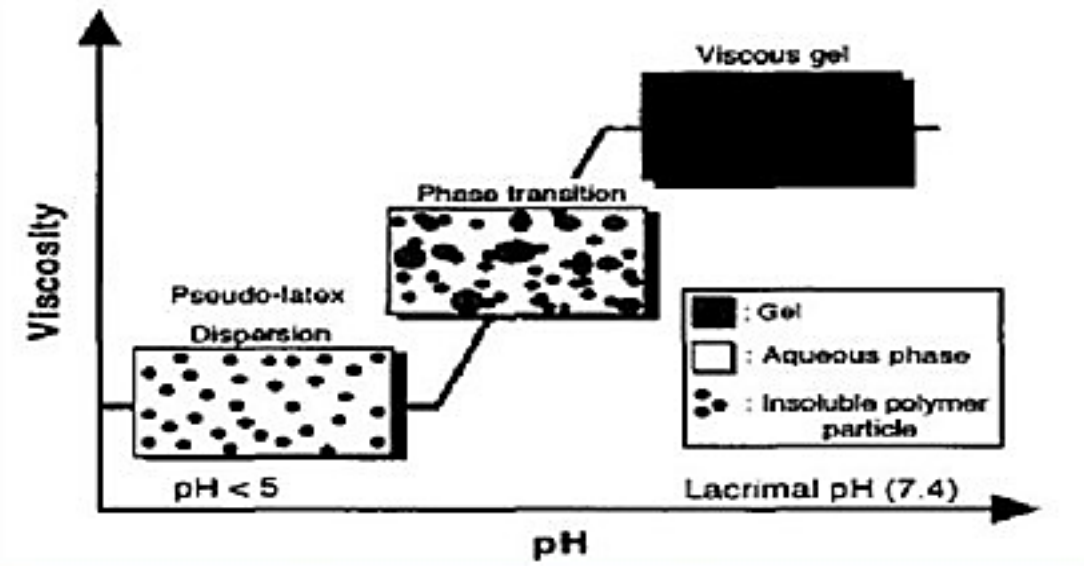

Figure. 4: Scheme of pH triggered in situ gel

3. ION TRIGERRED INSITU GELLING SYSTEM

In ion triggered in situ gelling system solution viscosity increases upon exposure to ionic concentration of the tear fluid. Ion sensitive polymer are able to crosslink with cations present in lacrimal fluid on ocular surface and enhance the retention time of drug [4].

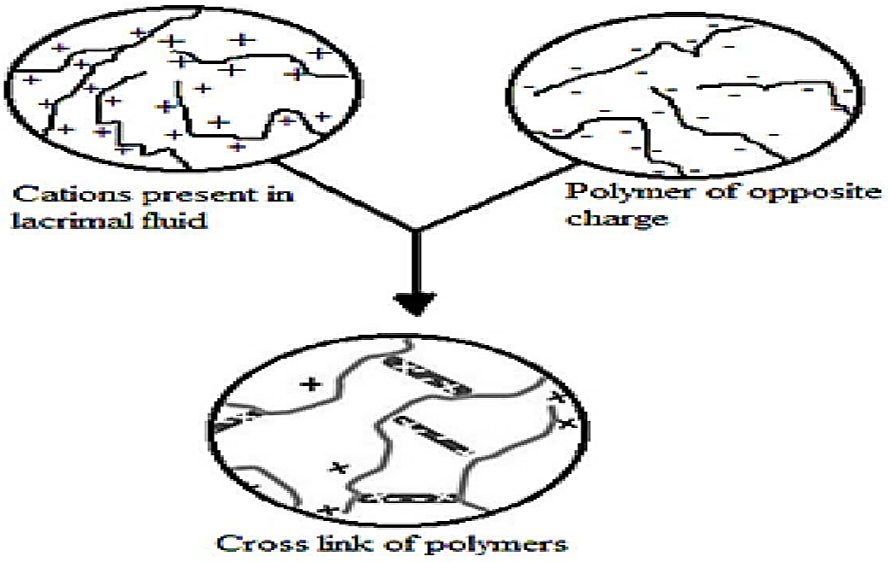

Figure.5: Schematic representation of ion triggered in situ gelling system

4. OSMOTICALLY INDUCED IN SITU GELLING SYSTEM

In this method, gelling of the solution instilled is triggered by changes in the ionic strength. It is assumed that the rate of gelation depends on the osmotic gradient across the surface of the

gel. The aqueous polymer solution forms a clear solution converts to a clear gel in the presence of the mono or divalent cations. The polymer which shows osmotically induced gelation includes gellan gum, alginates [5].

POLYMER USED IN THE FORMULATION OF IN SITU GEL

A polymer is a macromolecule composed of repeating structural units and these subunits are connected by covalent bonds.

IDEAL CHARACTERISTICS OF POLYMER IN PREPARATION OF INSITU GEL

1. Polymer capable of adhering mucous membrane.
2. Should be compatible and non-toxic.
3. Should have pseudo plastic behaviour.
4. Capable of decreasing the viscosity with increase shear rate.
5. Should influence the tear behaviour [6].

POLYMER CLASSIFICATION

Polymers are classified in different types on different basis as in the following enumeration.

1. CLASSIFICATION BASED ON THE SOURCE OF ORIGIN

Which is classified into three types:

• **Natural polymers:**

Polymers either obtained from plants or animal are called natural polymers. They are called plant and animal polymers.

E g: Cellulose, Jute, Lihen, Silk, Wool, Leather, RNA, DNA, Natural rubber.

• **Semisynthetic polymers:**

The polymers obtained by simple chemical treatment of natural fibres to improve their physical properties like lustrous nature, tensile strength is called semisynthetic fibres.

Eg: Acetate rayon, viscous rayon.

•**Synthetic fibres**:

The fibres obtained by polymerization of simple chemical molecules in laboratory are synthetic fibres.

E g: Nylon, terylene, polyethene, polystyrene, synthetic rubber, nylon, pvc, backlite, Teflon, Orion etc.

2. CLASSIFICATIONS BASED ON THE STRUCTURE

Which is classified into three types:

•Linear polymers:

In these polymers monomers are linked with each other and form a long straight chain. These chains have no any side chains. Their molecules are closely packed and have high density, tensile strength, and melting point.

Eg: Polyethene, PVC, Nylons, polyesters etc.

• Branched polymers:

They have a straight long chain with different side chains. Their molecules are irregularly packed hence they have low density, tensile strength, and melting point.

Eg: polypropylene (side chain —CH3), amylopectin and glycogen.

• Network or cross-linked polymers:

In these monomeric units are linked together to constitute a three-dimensional network. The links involved are called cross links. They are hard, rigid .and brittle due to their network structure,

Eg: Bakelite, Maia mine, formaldehyde resins, vulcanized rubber etc.

3. CLASSIFICATIONS BASED ON POLYMERIZATION PROCESS

They are two types as follows:

- **Addition polymers:**

The polymers formed by the addition of monomers repeatedly without removal of by products are called addition polymers. These polymers contain all the atoms of monomers

hence they are integral multiple of monomer unit. The monomeric units are generally alkenes and its derivatives.

Eg: Orion, Teflon, polyethene, polypropylene, PVC.

- **Condensation polymers:**

They are formed by the combination of two monomers by removal of small molecules like water, alcohol or NH3. They have ester and amide linkage in their molecules. Their molecular mass is not the integral multiple of monomer units,

Eg: Polyamides (Nylons), polyesters, polyurethanes.

4. CLASSIFICATION BASED ON MOLECULAR FORCES

Mechanical properties of polymers like tensile strength, toughness, elasticity depends upon intermolecular forces like van-der Waals forces and hydrogen bonding. On the basis of these forces, they are classified as

- **Elastomers**:

These are the polymers in which polymer chains are held up by weakest attractive forces. They contain randomly coiled molecular chains having few cross links. As the stain is applied polymer get stretched and as the force is released polymer regain its original position. These polymers are elastic and called elastomers,

E g: Neoprene, and vulcanized rubber.

- **Fibres**:

They have high intermolecular attractive force like H-bonding. They have high tensile strength and used in textile industries,

E g. Nylon-6, Nylon-66, and Terylene.

- **Thermoplastic polymers:**

These are the polymers having intermolecular forces between elastomers and fibres. They are easily moulded in desired shapes by heating and subsequent cooling at room temperature. They may be linear or branched chain polymers. They are soft in hot and hard on coding,

E g. Polythene, polystyrene, PVC.

- **Thermosetting polymers:**

This polymer is hard and infusible on heating. These are not soft on heating under pressure and they are not remoulded. These are cross linked polymers and are not reused,

E g. Bakelite.

5. CLASSIFICATION BASED ON THE HOMOGENEITY OF POLYMERS

- **Homopolymers:**

Homopolymers consists of only one type of repeating unit.

Eg: polymer (A)

- **Copolymers:**

Copolymers are polymers consisting of more than one type of repeating unit.

6. BASED ON TACTICITY POLYMER

It can be classified into 3:

- **Isotactic polymer:**

In this polymer, the arrangement of the characteristic polymer in the same side of the main chain.

- **Syndiotactic polymer:**

Polymer which has alternate arrangement of the side group is called as syndiotactic polymer.

- **Atactic polymer:**

Irregular arrangement of characteristic group around the main chain is called under gravity of atactic polymer. It possesses proper strength and more elasticity [4].

POLYMER PROPERTIES

1. CHEMICAL PROPERTIES

The attractive forces between polymer chains play a large part in determining polymer's properties. Because polymer chains are so long, these inter chain forces are amplified far beyond the attractions between conventional molecules. Different side groups on the polymer

can lend the polymer to (ionic bonding) or (hydrogen bonding) between its own chains. These stronger forces typically result in higher tensile strength and higher crystalline melting points. The intermolecular forces in polymers can be affected by (dipole) in the monomer units. Polymers containing (amide) or (carbonyl) groups can form (hydrogen bonds) between adjacent chains; the partially positively charged hydrogen atoms in N-H groups of one chain are strongly attracted to the partially negatively charged oxygen atoms in C=O groups on another. These strong hydrogen bonds, for example, result in the high tensile strength and melting point of polymers containing (Carbamate urethane) or urea linkages, which could be ascertained by polymerization interaction i.e., increasing of molecular weight as for instance [2].

2. OPTICAL PROPERTIES

Polymers such as PMMA and HEMA: MMA are used as matrices in the gain medium of solid-state dye lasers that are also known as polymer lasers. These polymers have a high surface quality and are also highly transparent so that the laser properties are dominated by the laser dye used to dope the polymer matrix. These types of lasers that also belong to the class of organic lasers are known to yield very narrow line widths which are useful for spectroscopy and analytical applications. An important optical parameter in the polymer used in laser applications is the change in refractive index with temperature. The optical properties were studied by UV-Vis Spectroscopy [2].

3. THERMAL PROPERTIES

A true workhorse for polymer characterization is thermal analysis, particularly Differential scanning calorimetry. Changes in the compositional and structural parameters of the material usually affect its melting transitions or glass transitions and these in turn can be linked to many performance parameters. For semi crystalline polymers it is an important method to measure crystallinity. Thermos gravimetric analysis can also give an indication of polymer thermal stability and the effects of additives such as flame retardants. Other thermal analysis techniques are typically combinations of the basic techniques and include differential thermal analysis, thermos mechanical analysis, dynamic mechanical thermal analysis, and dielectric thermal analysis. Dynamic mechanical spectroscopy and Dielectric spectroscopy are essentially extensions of thermal analysis that can reveal more subtle transitions with temperature as they affect the complex modulus or the dielectric function of the material [3].

4. MECHANICAL PROPERTIES

The characterization of mechanical properties in polymers typically refers to a measure of the strength of a polymer film. The tensile strength and Young's modulus of elasticity are of particular interest for describing the stress-strain properties of polymer films. Dynamic mechanical analysis is the most common technique used to characterize this viscoelastic behaviour. Other techniques include viscometry, rheometry, and pendulum hardness, the description of stress-strain behaviour is similar to that of metals [3].

POLYMER USED IN INSITU GEL

1. CARBOPOL

Carbopol are 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.

2. GELLANGUM

Gellangum is an anionic deacetylated exocellular polysaccharide secreted by pseudomonas elodea with a tetrasacharide repeating unit of one alpha-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.

3. 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 deliver.

4. 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 trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-Glucuronic 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.

5. 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 6.226. 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.

6. PLURONIC F-127

Poloxamers or Pluronic 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 ratio of 2:1, when these molecules are immersed into the aqueous solvents, they form micellar structures above critical micellar concentration.

They are regarded as PEO-PPO-PEO copolymers. Chemically they are Oxirane, methyl-, polymer with oxirane or α-Hydro-ω- hydroxypropyl (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. Pluronic 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 ™ F 127 is 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 hydroxylpropylmethylcellulose 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.

7. HYDROXY PROPYL METHYL CELLULOSE (HPMC)

HPMC is derived from a non-ionic component of cellulose ether, stable over a pH rage of 3.0-11. Hydroxy propyl methyl cellulose [HPMC] is a semi-synthetic polymer. It is used as a first choice in the construction of hydrophilic matrix systems as it provides a robust control of the drug release and the choice of viscosity ranges [7].

METHOD OF PREPARATION

In generally, two methods are used for the preparation of in situ gel.

1. Cold method
2. Hot method

1. COLD METHOD

In this method the drug is stirred with sufficient quantity of double distilled water and kept overnight at 4^{o}C in a refrigerator. The in situ gelling polymer is added slowly with continuous stirring. The dispersion is then stored in a refrigerator until clear solution is formed and finally volume is adjusted. This method is selected when poloxamer, chitosan or Carbopol is used as a gelling polymer. Considering the fact that polymeric dispersion of poloxamer remains as solution at lower temperature and gets converted into gel at higher temperature

because the solubility of polypropylene oxide chain of poloxamer decrease at high temperature which results in precipitation or salting out of polymer. similarly, chitosan also requires low temperature to remain as solution at room temperature, its hydrophobicity increase with increase in temperature.

2. HOT METHOD

This method is utilized when gellan gum or pectin is used as a gelling polymer. At higher temperature, gellan chains dissolve in water and assume a random coil conformation with a high segmental mobility at high temperature and remain as a solution at higher temperature. Sol-gel transition occurs on cooling gellan gum solution in the presence of ions like K^+ or Ca^{2+}. Similarly, pectin also requires higher temperature for its demethylation, which helps in the formulation of solution or dissolving of pectin [8].

EVALUATIONS OF IN-SITU GEL SYSTEM

Clarity, pH measurement, gelling capability, drug content, rheological study, in vitro diffusion study, isotonicity, antibacterial activity, in vivo visual testing in rabbits, and accelerated stability studies are all evaluation factors for in situ gel formulations. The formulation should have an optimal viscosity that enables easy instillation into the eye as a liquid (drops) that rapidly converts to a gel (initiated by pH, temperature, or ion exchange).

1. CLARITY

The clarity of formulated solution is determined by visual inspection under black & white Background.

2. TEXTURE ANALYSIS

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

3. pH OF GEL

pH can be determined formulation is taken in beaker & 1ml NaOH added drop wise with continuous stirring and pH is checked by using pH meter.

4. SOL-GEL TRANSITION TEMPERATURE AND GELLING TIME

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

5. GEL-STRENGTH

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

6. GELLING CAPACITY

In-situ gel is mix with simulated tear fluid (in the proportion of 25:7 i.e., application volume 25µl & normal volume of tear fluid in eye is 7µl) to find out gelling capacity of ophthalmic product. The gelation assessed visually by noting the time for & time taken for dissolution of the formed gel.

7. RHEOLOGICAL STUDIES

The viscosity measured by using Brookfield viscometer, cone & plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity 5-1000 mPas, before gelling & after ion gel activation by eye will have viscosity of from about 50-50,000 mPas.

8. ISOTONICITY EVALUATION

Isotonicity is important characteristics of ophthalmic preparation. Isotonicity is maintained to prevent tissue damage or irritation of eye. All ophthalmic preparation is subjected to isotonicity testing, science they exhibited good release characteristics & gelling capacity & the requite velocity. Formulation mixed with few drops of blood & observed under microscope at 45x magnification & compared with standard marketed ophthalmic formulation.

9. SWELLING STUDIES

Swelling studies are conducted with a cell, equipped with thermos jacket to maintain a constant temperature. The cell contains artificial tear fluid (composition – 0.67g Nacl, 0.20g $NaHCO_3$, 0.008g $CaCl_2.2H_2O$& distilled water q.s to 100g). Swelling medium equilibrating at 37^0. One millilitre of formulated solution is placed in dialysis bag & put into the swelling medium. At specific time interval the bag is removed from the medium & weight is recorded. The swelling of the polymer gel as a function of time is determined by using the following relationship.

$$\% S_t = (W_t - W_0)\ 100/W_0$$

Where,

W_0=Initial weight of gelling solution.

W_t=Final weight of gel.,

S_t = Swelling at time's'

10. OCULAR IRRITANCY STUDIES

Ocular irritancy studies are performed on male albino rabbits, weighing 1-2 kg. The modified Draize technique is used for ocular irritation potential of ophthalmic products. The formulation is placed in lower cul-de-sac & irritancy is tested at time interval of 1hr, 2hrs, 48hrs, 72hrs, & 1 week after administration. The rabbits are observed periodically for redness, swelling, & watering of eyes.

11.ANTIMICROBIAL ACTIVITY

Antimicrobial efficacy studies are carried out to ascertain the biological activity of sol-gel-system against microorganisms. This is determined in agar diffusion medium employing 'Cup Plate Techniques'. The microbial growth of bacteria is measured by conc. of antibiotic & compared with that produced by known conc. Of standard preparation of antibiotic & carried out the microbial assay serial dilution method is employed.

12.STERILITY TESTING

Sterility testing is carried out as per the IP 1996. The formulation is incubating for not less than 14 days at 30^0- 35^0 C in the fluid thioglycolate medium to find the growth of bacteria & at 20^0-25^0C in Soya bean casein digest medium to find the growth of fungi in formulation.

13. ACCELERATED STABILITY STUDIES

Formulation is replaced in amber coloured vials & sealed with aluminium foil for the short term accelerated stability study at 40± 20 c & 75 ±5% RH as per International Conference of Harmonization (ICH) State Guidelines. Sample is analysed at every month for clarity, pH, gelling capacity, drug content, rheological evaluation & in vitro dissolution [9].

MARKETED PRODUCT OF OPTHALAMIC IN SITU GEL [11]

PRODUCT NAME	DRUG USED	MFG.COMPANY
Timoptic-XE	Timolol maleate	Merck and Co. Inc
Cytoryn	Interleukin-2	Macromed
Azasite	Azithromycin	Insite vision
Akten TM	Lidocaine hydrochloride	Akten
Pilopine HS	Pilocarpine hydrochloride	Alcon laboratories inc

CONCLUSION

In situ gels offer the primary requirement of a successful controlled release product that is increasing patient compliance. Exploitation of polymeric in situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in-situ gel dosage forms very reliable. In situ activated gel forming systems seem to be preferred as they can be administered in drop form and create significantly less problems with vision. Moreover, they provide good sustained release properties. Over the last decades, an impressive number of novel temperatures, pH, and ion induced in-situ forming solutions have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular hydrogel depends on its intrinsic properties and envisaged therapeutic use. Future use of biodegradable and water-soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems [10].

REFERENCES

1. HB N, Bakliwal SR, Pawar SP. In-situ gel: new trends in controlled and sustained drug delivery system.Int J Pharmtech Res 2010;2:1398-408
2. Wu Yumei, Liu Yuanyuan, Li Xinyue. Asian journal of pharmaceutical science,2019;14[1]:1-15.
3. Patel A and Cholkar K.World Journal of Pharmacology,2013;2(2):47-64.
4. Dibyalochan Mohanty, Dr Vasudha Bakshi, Nandini Simharju, Chinmaya Keshari Sahoo, Akiful Haque. International Journal of Pharmaceutical Science Review and Research,2018;50(1):175-181.
5. A P Patil et al. International Journal of Pharmaceutical Science and Research,2012;3(9):2938-2946.
6. Pallavi Chand, PratibhaGnanarajan, Preeti Kothiyal. Indian Journal of pharmaceutical and biological research,2016;4(2):11-19.
7. Parekh Hejal. Journal of Drug Delivery and Therapeutics,2012;2(5):136-145.
8. Nirmal H B et al. International Journal of Pharma Tech Research,2010;2(2):1398-1408.
9. Therese Nimi N, Deepa Manohar R. Journal of Pharmaceutical Science and Research,2019;11(7):2585-2589.
10. K S Rathore. International Journal of Pharmacy and Pharmaceutical Science,2010;4(2):30-34.
11. Sarika Meshram, Santhosh Throat. Scholars academic journal of pharmacy,2015;4(7):340-346.
12. Asmat Majeed and Nisar Ahmed khan. Journal of Drug Delivery and Therapeutics,2019;9(1):337-347.