



CURRENT ASPECTS IN OCULAR POLYMERIC IN-SITU GELLING SYSTEM.

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Article Received on 17/02/2016

Article Revised on 07/03/2016

Article Accepted on 27/03/2016

ABSTRACT

Eye is a sensitive organ can easily injure and infected. Eye diseases are commonly encountered in a day to day life. Ocular drug delivery is one of the most interesting and challenging area for scientists due to its unique anatomy and physiology that includes various types of barriers such as different layers of cornea, sclera and retina including blood retinal barriers and blood aqueous barriers, conjunctival and choroidal blood flow etc. Conventional dosage form like ointments, solutions and suspensions show drawbacks such as rapid pre-corneal elimination of drug, high difference in efficiency and blurred of vision. To overcome these problems newer drug delivery system like *In situ* gel has been developed. *In situ* gels are liquid during installation and phase transition is occurs in the ocular cul-de-sac to form viscoelastic gel and this gel provides a response when environmental changes (pH, temperature and ion exchange) take place. It enhances the drug residence time and improves its ophthalmic bioavailability into an anterior chamber of the eye. Various biodegradable polymers like carbopol, pluronics, alginate, gelrite etc. are used. *In situ* gelling system is a convenient, easy to administer and has better patient compliance. Formulation were evaluated for physical parameters like clarity, pH, drug content, gelation, sterility test, ocular irritancy study, in vitro drug release and rheological studies. It was observed that as the concentration of polymer increases, the rate of drug release decreases to produce sustained drug delivery for prolonged period of more than 8 hours.

KEYWORDS: *In situ* gel, Sol-gel, Hydrogel, Ion triggered, Temperature triggered and pH triggered.

INTRODUCTION

From last 30 years greater attention has been given on development of controlled and sustained drug delivery systems.^[1] Ophthalmic drug delivery is a most challenging and interesting area for upcoming pharmacists and formulation chemists due to its unique anatomy and physiology, which consists of three layers namely: Epithelium, Stroma, and Endothelium. Epithelium is outer layer of eye which acts as a barrier for hydrophilic drug, while lipophilic drugs facing difficulties to cross the stroma. Endothelium layer is lipoidal in nature.^[2] There are about 70% conventional dosage forms are available in the market.^[3] Ophthalmic solutions has poor bioavailability and therapeutic response, because of high tear fluid turnover and dynamics that cause rapid precorneal elimination of the drug. A high frequency of ophthalmic solutions instillation is main cause of patient non-compliance. Addition of excess drug in the formulation is an attempt to overcome bioavailability problems is associated with serious side effects if the drug solution drained from the eye is systemically absorbed from the nasolacrimal duct. Various other ophthalmic dosage forms such as ointments, suspensions, inserts and aqueous gels have been developed in order to enhance the ophthalmic

bioavailability. This ocular drug delivery system however has not been used frequently because of some disadvantages such as blurred vision from ointments or low patient compliance from inserts.^[4]

In recent few years, there has been significant research efforts are taken on ocular drug delivery system which provides sustained and controlled drug release.^[5] This type of drug delivery system is more desirable dosage form where drug can administer in solution form with little or no problem like blurred vision and frequently dosing are also not need. *In situ* drug delivery system is liquid during installation, undergoes phase transition to viscous gel in accordance to physiological condition like pH, temperature and electrolyte composition. This phase transition occurs via cross linking of polymer chain that can be achieved by covalent bond formation (chemical cross linking) or non covalent bond formation (physical cross linking).^[6]

Advantages of *In situ* gelling system^[5]

- Ease of administration and good patient compliance.
- It shows increased drug gastric retention with slow drug release.
- *In situ* gelling system reduces dosing frequency.

- It shows local action and site specificity by directly action onto the targeted site.
- It shows less adverse effects compared to other pharmacological dosage forms.^[7,8]
- Improve drug bioavailability.

Disadvantages of *In situ* gelling system^[1]

- Stability problems due to chemical degradation.
- It requires high level of fluids.
- Degradation can occur due to storage problems.
- Blurred vision and matted eye lids.

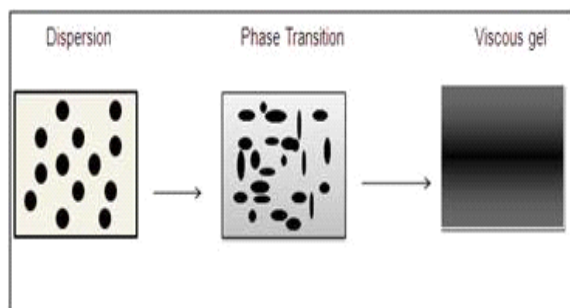


Figure 1: Mechanism of sol-gel transition.

Table 1: polymers used for ocular *In situ* system^[6]

Polymer	Origin	Charge	Solubility	Mucoadhesive Capacity
Carbomer	Synthetic	Anionic	Insoluble	+++
Polyacrylic acid	Natural	Anionic	Insoluble	+++
Chitosan	Natural	Cationic	Soluble	++
Xanthan gum	Natural	Anionic	Insoluble	+
Methyl cellulose	Natural	Non-ionic	Soluble	+
Xyloglucan	Natural	Anionic	Soluble	+
Poloxamer	Synthetic	Non-ionic	Soluble	++
Sodium alginate	Natural	Anionic	Soluble	++
HPMC	Natural	Non-ionic	Soluble	+
Mucoadhesive capacity: Excellent(+++), Good(++), Poor(+)				

THE ANATOMY OF HUMAN EYE^[9]

The human eye is a complex structure designed to collect the information about the environment around us. The eye is an important and essential sensory organ of the body that converts light to an electric signal, send to the brain that treat and interpret the information. Eye has ability to refract light and produce a focused image that stimulates nervous system and enable the ability to see a proper image. Briefly, the eye ball is covered by three layers: Sclera and Cornea (an outer fibrous protective layer), Choroid (a middle vascular layer) and Retina (inner nervous layer). The stroma is the only hydrophilic layer. The eye is divided into two parts: 1) the anterior and 2) the posterior chamber. The anterior segment includes the cornea, ciliary body, sclera, and the lens. The anterior chamber totally filled with the aqueous humor. The posterior segment includes all other the structures between the lens and the optic nerve.

Ideal Characteristics of Polymers^[5]

- It should have good tolerance.
- It should be biocompatible.
- It should have pseudo plastic behaviour.
- It should have capability of adherence to mucus.
- Polymer should be capable of decreasing viscosity with increasing shear rate there by lowering viscosity during blinking eye.

Structure and different parts of eye^[10,11]

Aqueous Humour

Aqueous humour is an area between the cornea and the front surface of the lens is called the aqueous humour. Anterior chamber is filled with aqueous humour which is a jelly like substance.

Choroid

It absorbs unused radiation and located behind the retina. The choroid is the vascular coat of the eye and is divided into four layers.

- Supra choroids
- Layer of vessels
- Chorio capillaries
- Bruch's membrane

Ciliary Muscle

The ciliary muscle is attached to the iris and it is ring-shaped muscle. Shape of the lens is mainly depends up on contraction and relaxation of ciliary muscle.

Cornea

The cornea is a unique biological tissue that does not contain blood vessels and it is transparent to light. It is composed of five layers: epithelium, Bowman's layer, stroma, Descemet's membrane and endothelium. In front of the eye is a small transparent dome around 11mm (0.43in) in diameter and 500µm thick at the center, and at periphery thickens to around 700µm. The primary function of the cornea is transmitting and focusing light into the eye.

Fovea

It is a small depression in the retina (approx. 1.5 mm in diameter). With the help of fovea high resolution vision of fine is possible.

Hyaloids

It acts as a diaphragm which separates the aqueous humor from vitreous humor.

Iris

The iris is the colored part of the eye and extends from the ciliary body anteriorly, observed behind the cornea and posteriorly in front of the lens. It divides the anterior segment of the eye into two chambers namely anterior and posterior chambers which are filled with aqueous fluid secreted by the ciliary body. The iris is supplied by parasympathetic and sympathetic nerves. Contraction and relaxation (dilation) of pupil is mainly due to parasympathetic and sympathetic stimulation.

Lens

Similar to cornea, lens is also transparent for light. It is a flexible unit having ability to change its shape in order to enhance or reduce the amount of refracting light rays in to the eye. It is suspended by zonule fibers from the ciliary muscles.

Optic Nerve

It is the second cranial nerve, responsible for vision. Each nerve contains about one million fibers transferring information from the rod and cone cells of the retina.

Papilla

Papilla is located at the position where the optic nerve leaves the retina. It is also known as "Blind spot."

Pupil

This is formed by the iris. As the size of the iris increases pupil size decreases, and as the size of iris decreases the pupil size will increase.

Retina

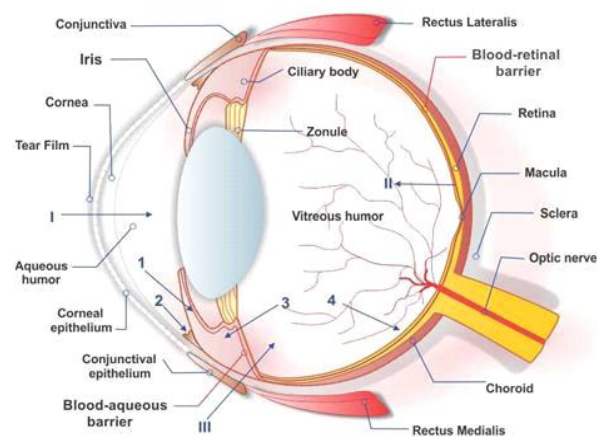
The retina can also be described as the "screen" because an image is formed on retina. The retina has photosensitive elements (i.e. rods and cones) which convert the light into nerve impulses. The retina senses the light and generates impulses which are received by the brain through the optic nerves.

Sclera

It is a thick, tough, white outer covering of the eye ball. It consists of a membrane which maintains proper shape of the eye.

Vitreous Humour

The vitreous humor (vitreous body) is a jelly-like substance that fills the posterior portion of the eye. Vitreous humor is a clear gel comprised of collagen fibrils in a network of hyaluronic acid. With aging, the gel starts to liquefy and shrink. When this happens, aqueous fluid goes from the anterior chamber into the posterior chamber of the eye.



Anatomy of human eye.

ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEM^[4,5]

- Needle free (invasive) drug delivery system.
- Self medications no need to have trained person to administer the drug. So that patient compliance improved as compared to parenteral route of drug administration.
- It bypasses the hepatic first pass metabolism which causes the reduction in dose of drug as compared to oral route.
- Good bioavailability of hydrophilic and low molecular weight drugs can be obtained through ocular drug delivery.
- Rapid drug absorption because of high vascularization and large surface area available for absorption.
- Ocular administration of drug is a useful therapy in many cases compared to other routes.

DISADVANTAGES OF OCULAR DRUG DELIVERY SYSTEM^[12,13]

- Low absorption of drug due to presence of various barriers which reduces permeability of drug.
- Various systemic side effects are generated due to drainage of major portion of drug into the lacrimal duct.
- Frequent dosing due to rapid elimination of drug by tear fluid and the blinking of eye.

BARRIERS FOR OCULAR DELIVERY

• Loss of drug from the ocular surface

Normally the turnover of lachrymal fluid is only 1 $\mu\text{l}/\text{min}$ and the excess instilled volume of drug is drained out by the lachrymal fluid which flow through nasolacrimal duct rapidly. Systemic absorption of drug rather than ocular absorption is another source of loss of drug. Systemic absorption takes place by two ways: by either from conjunctiva via blood capillaries or by the solution flow through nasal cavity.^[9]

• Lachrymal fluid-eye barriers

Corneal epithelium limits paracellular drug penetration due to its cells form tight junctions. Therefore lipophilic drugs have higher permeability through the cornea than the hydrophilic. Generally conjunctiva has 20 times greater surface area and leakier epithelium than the cornea.^[9]

• Blood-ocular barriers

Blood-ocular barriers protect the eye from xenobiotics which present in blood stream. Blood-aqueous and blood-retinal barrier, these are two types Blood-ocular barriers present in eye. The anterior of blood-eye barrier is made of endothelial cells in the uvea (It includes the ciliary body, iris, and choroid). This barrier prevents the entry of plasma albumin into the aqueous humor. Posterior barrier between blood stream and eye is made of the tight walls of retinal capillaries and retinal pigment epithelium (RPE). Retinal capillaries has extensive blood flow and leaky walls. Drugs easily enter into the choroidal extravascular space, but after that distribution into the retina is limited due to the retinal pigment epithelium and retinal endothelia.^[14,15]

OPHTHALMIC DISORDERS^[9]

Eye Infections

Eyes can infect by bacteria, viruses or fungi. Infections of eye may occur in different parts of either same or in both eyes at a same time. Common eye infections are corneal ulcers, conjunctivitis & Endophthalmitis.

1) Conjunctivitis

Conjunctivitis is nothing but inflammation (swelling) or infection of conjunctiva (membrane lining of the eyelids). It is caused by cellular infiltration. Common bacteria like *Staphylococcus aureus* is a main cause bacterial conjunctivitis and blepharo-conjunctivitis. Many other organisms like *Streptococcus pneumoniae*, *Haemophilus influenza* also cause conjunctivitis.

Classification of Conjunctivitis

- (1) Infective – Acute, Sub acute & Chronic
- (2) Allergic conjunctivitis.

2) Corneal ulcers / Keratitis

Inflammations of cornea are also known as Keratitis which is characterized by corneal oedema, ciliary congestion and cellular infiltration. Cornea is the most anterior part of eyeball, direct contact of cornea to

external environment and hence more chances to get infected easily. Most virulent organisms caused the Bacterial corneal ulcers. List of bacteria associated with corneal ulceration are: *E.coli*, *Staphylococcus aureus*, *Pseudomonas pyocyanea*, *Proteus* etc.

3) Endophthalmitis

It is severe type of infection of intraocular inflammation (purulent uveitis) including ocular cavities & inner coats of eyeball. Causative organisms are endophthalmitis include *pseudomonas*, *E.coli*, *Streptococci* and etc. Generally antimicrobials like antibacterial, antivirals and antifungals are used in prevention and treatment of endophthalmitis. Some Commonly used antibacterials in the treatment of ocular infectious include sulfonamides, aminoglycosides, and polymyxin-based combinations.

PROTECTIVE MECHANISM OF EYE^[9]

The eye have efficient protective mechanisms like drainage, reflex blinking and lachrymation, while eye lid closure protects the eye from external aggression. The drug in suitable type of dosage form, upon instillation, eye stimulates the protective physiological mechanisms, i.e., tear production, which exert defence against ophthalmic drug delivery. Another most important problem of the removal of topically administered drugs from the precorneal area is the nasal cavity. As compare to cornea the nasal mucosal membrane has greater surface area and higher permeability. Generally ophthalmic conventional solution normal dropper used to delivers about 50-75 μl per drop and maximum portion of these drops rapidly drain out until the eye is back to normal resident volume i.e. 7 μl . Due to this drug loss in front of the eye, very small drug is available to enter the cornea and inner tissue of the eye. Tears wash the surface of the eye permanently and exert an anti-infectious activity with the help of immunoglobulin and lysozyme they contain. Finally, the lachrymal fluid is drained down the nasolacrimal pathways. All these protective mechanisms are responsible for the extensive and fast precorneal loss of topically applied ophthalmic drugs.

Gels^[16]

Gels may be defined as an intermediate state of matter which containing both solid and liquid components. It contains three dimensional solid networks. Gels are classified into two types based on the nature of the bonds. They are

- Physical gels: It arise when weak bonds like hydrogen bonds, electrostatic bonds and van der waal bonds constitute together to form the gel network.
- Chemical gels: this type of gels are arise when strong covalent bonds constitute to maintain the gel network. In chemical gels network cross-links are present which help reduce dissolution of hydrophilic polymer in water.

Hydrogel^[2]

Aqueous gel (hydrogel) consist of hydrophilic high molecular weights, cross-linked polymers or co-polymers that form a three-dimensional network in water. These gels have been shown to combine significantly longer residence times in the cul-de-sac with increased drug bioavailability. Kim et al define the hydrogels contain polymers which have the ability to swell in water or aqueous solvents and induce a liquid-gel transition. The efficacy of ophthalmic dosage form is mostly based on an ocular residence time via enhanced viscosity and mucoadhesive properties.

IN SITU GEL^[2]

In situ gel is a polymeric solution which can be administered as liquid & undergoes a phase transition from liquid to semisolid gel upon exposure to physiological condition. The gelation can be triggered by change in temperature, pH or ions.

Classification of *In situ* gelling system

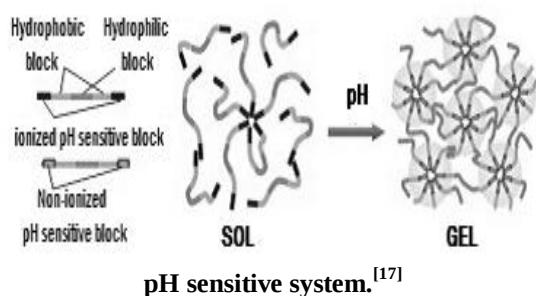
1. pH sensitive *In situ* gelling system
2. Temperature sensitive *In situ* gelling system
3. Ion sensitive *In situ* gelling system

1. pH sensitive *in situ* gelling system^[17]

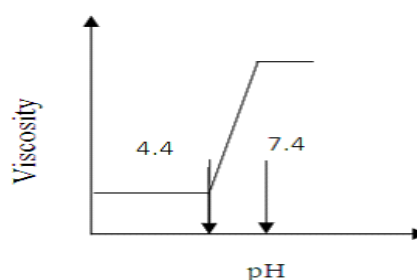
Conversion of solution to gel is triggered by a change in the pH. Cross linked acrylic acid and derivatives such as Carbomer, cellulose acetate phthalate latex are used for this system. Cellulose acetate derivatives are the only polymer known to have a buffer capacity to form gel effectively in the cul-de-sac of the eye. Gel is formed at eye when pH raised from 5 to 7.4.

Mechanism^[6]

All pH sensitive polymers contain both acidic or basic groups that can either donate or accept protons in response to changes in pH. In case of weakly acidic group, as the pH of eye increase, swelling of hydrogel increases, while swelling of hydrogel decreases in case of weakly basic groups.



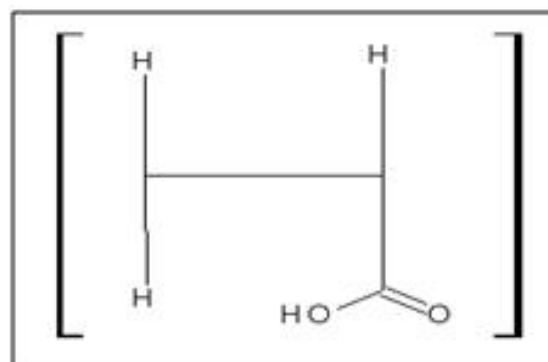
pH Sensitive gels



Graphical representation of pH sensitive in situ gelling system^[6]

Polymers used in pH sensitive *In situ* gelling system:

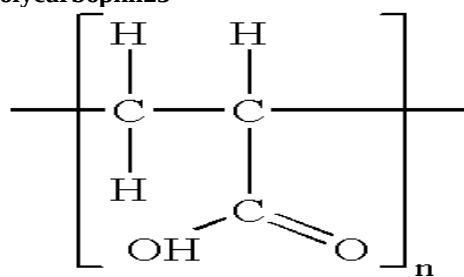
- Carbomer^[6]



Structure of Carbomer

Mucoadhesive property of carbomer is due to hydrogen bonding, hydrophobic interaction or electrostatic interaction. Molecules of Carbopol are tightly coiled acidic molecule. when dispersed in water, carboxylic group of that molecule partially dissociates (COO^- and H^+) to form flexible coil. Polymers which are pH sensitive, swells as pH is increases. In acidic medium, due to hydrogen bonding it is in collapsed state, as the pH increases, repulsion occur between the anionic groups (COO^-), which results in gel swelling. The gelling is activates in two stages: Dispersion and hydration of carbopol, sodium hydroxide, potassium hydroxide or triethanolamine add to neutralize the solution. Irritation to eye occurs as the concentration of caropol increases because of its acidic nature. To overcome on this problem viscosity enhancer like hydroxyl propyl methyl cellulose(HPMC), methyl cellulose(MC) are added. It do not affect the gelling property of polymer.

- Polycarbophil^[6]



Structure of polycarbophil

Polycarbophil is polyacrylic acid derivative obtained from natural origin having lightly cross linking property. It also have excellent mucoadhesive property.

Mechanism^[6]

Polycarbophil is water insoluble but due to its swelling capacity in neutral medium permits the cross linking of polymer chain with mucus layer. Polycarbophil contain carboxylic acid group bind to mucin with hydrogen bond. Noveon®AA-1 polycarbophil, is a high molecular weight polyacrylic acid polymer entanglement with divinyl glycol and shows sol-gel transition.

2. Temperature sensitive *In situ* gelling system^[3]

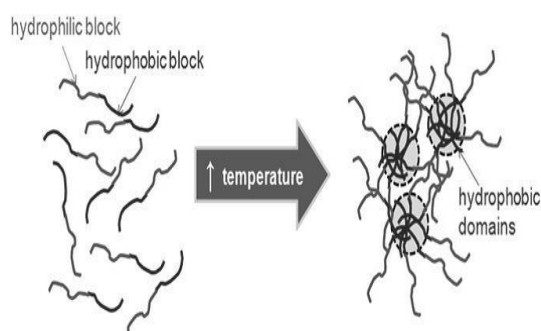
In this system liquids are in solution form at room temperature (25-27°C) and undergo phase transition when it come in contact with body temperature (35-37°C) due to change in temperature.

Temperature sensitive gels are three types;

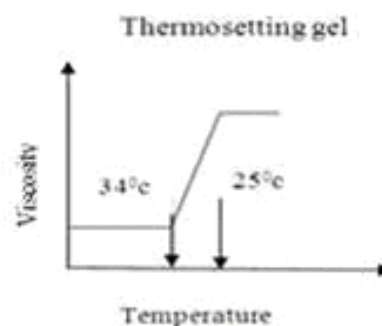
- **Positive temperature sensitive gel**
positive temperature sensitive gel has upper critical solution temperature(UCST), such gels get contract when temperature go below THE UCST.
- **Negative temperature sensitive gel:** this type of gel has LCST (Lower critical solution temperature), and gel get contract on heating above LCST.
- **Thermally reversible gel:** At higher temperatures; these polymers develop a random coil conformation in solution. Upon cooling, it comes in original state.

Mechanism^[18]

Here increase in temperature cause sol-gel phase transition. This conversion occurs by three mechanisms: polymer desolvation, increased micellar aggregation and cross linking of polymeric network. When temperature of solution increases polymer chain degradation occurs which lead to hydrophobic domain formation and followed by phase transition(liquid to hydrogel) take place.



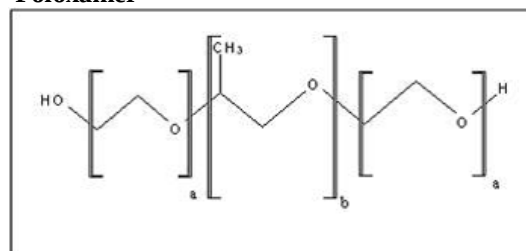
Mechanism of temperature sensitive system.^[17]



Graphical representation of temperature sensitive *In situ* gelling system.

Polymers used in temperature sensitive gelling system

• Poloxamer^[6]

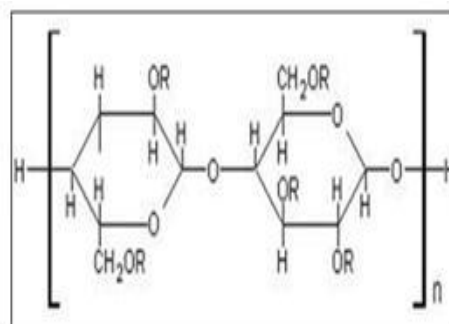


Structure of Poloxamer

Mechanism of gelling action

Poloxamer consists of two part from which one is hydrophobic part (polypropylene oxide) located centrally, surrounded by hydrophilic part (polyethylene oxide). It behaves like viscous liquid at room temperature (25°C), as the temperature increases (37°C) transparent gel form. Below the body temperature it forms small micellar subunit in solution and when reaches to body temperature (37°C) results in swelling of polymers leads to form large micellar cross linked network.

• Cellulose derivative^[19]

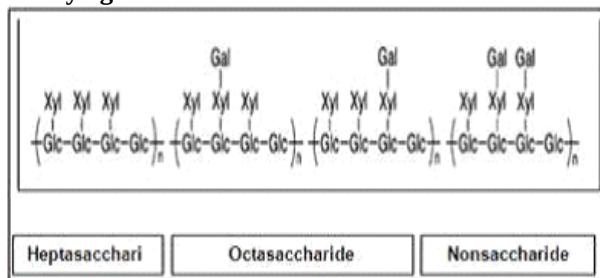


Structure of HPMC

Mechanism

Here hydrophobic interaction between molecules containing methoxy substitution causes the gellation of cellulose solution. At low temperature initially molecules get hydrated and little polymer-polymer interaction occurs. And at high temperature, polymers lose their water of hydration.

- Xyloglucan**



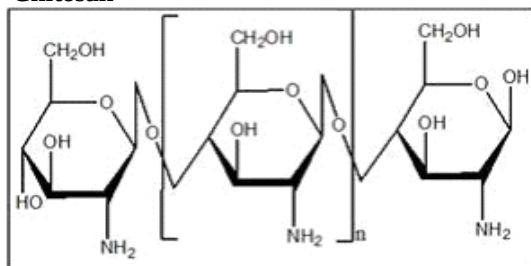
Structure of Xyloglucan

Xyloglucan is a polysaccharide, obtained from tamarind seeds and is made of a (1, 4)-β-D-glucan backbone chain with (1, 6)-α-D-xylose branches that are partially substituted by (1,2)-β-D-galactoxylose. Partial degradation of xyloglucan takes place by the enzyme β-galactosidase. The resultant product having thermally reversible gelation activity. Means xyloglucan form thermally reversible gel when temperature reaches to body temperature.^[20]

Mechanism^[6]

When it's dilute solution heated and solution to gel transition take place due to partial degradation of β-galactosidase. The transition temperature is inversely proportional to galactose removal ratio and polymer concentration.

- Chitosan**



Structure of Chitosan

Chitosan is a thermosensitive, biodegradable, polycationic polymer obtained by alkaline deacetylation of chitin, which is a natural component of shrimp and crab shell. Chitosan is a pH dependent cationic polymer, up to pH 6.2 it remains in dissolved form in aqueous solutions. As the pH of aqueous solution of chitosan reaches neutral pH gel like precipitate.

By addition of polyol salts (having a single anionic head such as sorbitol, glycerol, fructose or glucose phosphate salts) to chitosan aqueous solution, the pH gelling cationic aqueous solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any cross linking or any chemical modification.^[20]

Mechanism^[6]

Chitosan have mucoadhesive property due to ionic interaction between amino group of chitosan (positively

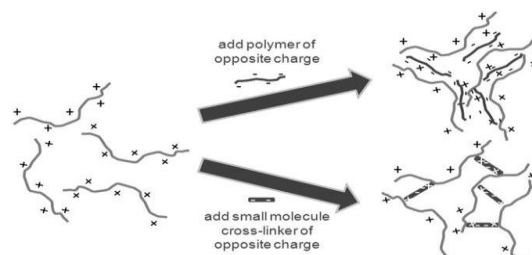
charged) and sialic acid residue of mucins (negatively charged), depending upon environmental pH. It is used in preparation of artificial tear formulation as viscosity enhancer because of its hydrophilic, good spreading and bioadhesive property.

3. Ion Sensitive Gelling System^[17]

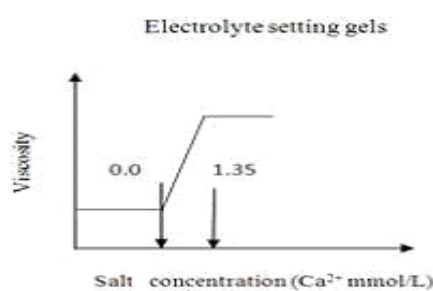
In ion sensitive gelling system solution to gel phase transition is triggered by cations like Na⁺, Ca⁺⁺ and Mg⁺ which are present in tear fluid of the eye. Generally in this type of drug delivery system anionic polymers are used in formulation. Polymers like alginate, gellan gum, gelrite and tamarind gum are used in preparations. Some other polymers like methyl cellulose (MC) and hydroxyl propyl methylcellulose (HPMC) are also used in combination to other polymer to enhance effect. They provide sustained drug release by enhancing mucoadhesiveness.

Mechanism^[6]

Mechanism of gel formation is based on interaction between ions of polymer and divalent ions of tear fluid. When cationic tear fluid comes in contact with anionic polymer, phase transition occurs and viscose gel forms.



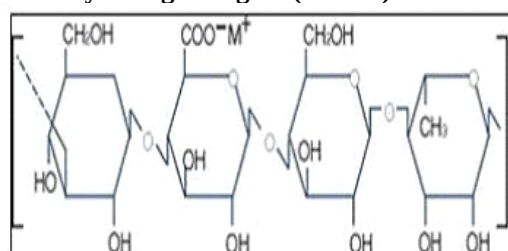
Mechanism showing Ion activated system.^[17]



Graphical representation of ion activated *in situ* gelling system.

Polymers used for ion sensitive *In situ* gelling system

- Deacetylated gellan gum (Gelrite)**

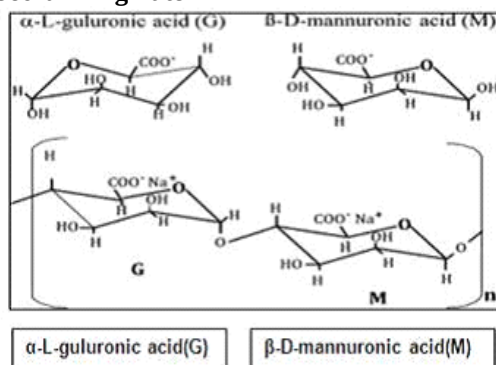


Structure of Gelrite

Mechanism^[6]

Gellan gum also known as gelrite produce a cation induced *in situ* gelation (Ca^{2+} , Mg^{2+} , K^{+} , Na^{+}) due to ionic interaction between negatively charged helices of polymers and mono or divalent cations (Na^{+} , Ca^{+} , Mg^{+}) of tear fluid. Divalent ions superior to promoting gel formation as compared to monovalent cations. Gelation cause prolongation of the residence time of drug at site of absorption and improve drug bioavailability.

- Sodium Alginate^[20]**



Structure of sodium alginate

Alginic acid or salts alginate are a linear block copolymer polysaccharide made of α -L-glucuronic acid and β -D-mannuronic acid residues combined together by 1, 4-glycosidic linkages. Depending on algal source, arrangement along the molecules and proportion of each block is vary. Dilute aqueous solutions of alginic acid form firm gels when it come in contact with di and tri valent metal ions. Alginic acid can be selected as a vehicle for ophthalmic preparations, because it exhibits favorable biological properties such as nontoxicity, biodegradability, mucoadhesiveness and improved residence time.

Mechanism^[6]

β -D-mannuronic acid (M) and α -L- glucuronic acid (G) are monomers of alginic acid. These monomers are arranged as M-M block or G-G block with alternating sequence M-G block. When G block of polymer interact with calcium moieties of tear fluid resulting in the formation of homogenous gel. Porosity and mechanical strength of hydrogel depends on G:M block ratio, type of cross linker used and concentration of alginate solution.

Advantages of Ocular *In Situ* Hydrogel^[3]

- Easy to manufacture and hence less complex process and reduces cost of Manufacturing.
- Reduced drug concentration in formulation.
- Reduction in dosing frequency.
- Enhance Patient acceptability.
- These type of drug delivery system is more comfortable than insoluble or soluble insertion.
- Improved bioavailability due to-
 - a). Decreased nasolacral drainage of the drug
 - b). Increased precorneal residence time.

- Reduced in side effects which arise due to systemic absorption of the drug through naso-lacimal duct.

Limitations of Ocular *In Situ* Hydrogel^[3]

- Matted eyelids.
- Blurring of vision.
- Limited values in terms of improvement of bioavailability.

Drug release from hydrogels^[9]

Hydrogel have number of characteristics that make them useful in drug delivery applications. Hydrogel is hydrophilic in nature, can absorb large amount of water. So that the drug release mechanism from gels are totally different from hydrophobic polymer system. Both simple and sophisticated models were previously developed to determine the drug release from a hydrogel. These models are mainly divided into 3 categories: diffusion controlled, swelling controlled and chemically controlled mechanism. (Fig 1).

- Diffusion controlled: Drug diffusion from the non-degraded polymer.
- Swelling controlled: Enhanced drug diffusion due to polymer swelling.
- Chemically controlled: drug release due to polymer degradation and erosion.

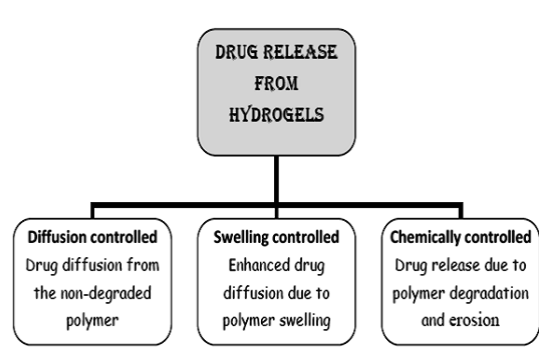


Figure 1: Drug release from hydrogen.

CHARACTERIZATION AND EVALUATION OF *IN SITU* GELLING SYSTEM:-

With the help of following parameters in-situ gel is evaluated and characterised-

1. CLARITY^[21]

The clarity of the gel is determined after and before gelling by visual inspection under light against black and white backgrounds alternatively.

2. TEXTURE ANALYSIS^[22]

The instrument like Texture profile analyzer is used to assessed the cohesiveness, consistency and consistency of in-situ gel, which mainly indicates the easiness in administration and gel strength.

3. pH OF GEL^[22]

pH can be determined by taking formulation in beaker & adding 1ml sodium hydroxide (NaOH) slowly (drop

wise) with continuous stirring. pH meter is used to check the pH of formulation.

4. GELLING CAPACITY^[2]

To determine gelling capacity, *In situ* gelling formulation is mix with simulated tear fluid (in the proportion of 25:7 i.e. gelling formulation volume 25µl & normal tear fluid in eye is 7µl). The gelation assessed visually by noting the time taken for dissolution of the formed gel.

Composition of simulated tear fluid.^[22]

Sodium bicarbonate: 0.20gram

Sodium chloride: 0.67gram

Calcium chloride dehydrate: 0.08gram

De ionized water: 100ml

5. RHEOLOGICAL / VISCOSITY STUDIES^[2,20]

This is an important parameter for evaluation. The viscosity measured by using cone and plate viscometer, Brookfield viscometer. Formulation of in-situ gel is placed in sample tube. Formulation should have viscosity before and after gel activation around 5-1000 mPas and 50-50,000 mPas respectively. The viscosity of *In situ* gel formulation should be such that no difficulties are arises during administration into eye.

6. ISOTONICITY EVALUATION^[2]

Isotonicity is important parameter of ophthalmic preparation. Isotonicity of preparation is maintained to prevent irritation and tissue damage of eye. Test can be done by mixing formulation with few drops of blood and observed under microscope at magnification 45x. All ocular formulation is subjected to isotonicity testing, even they exhibiting good gelling capacity and drug release characteristics.

7. SWELLING STUDIES^[2]

Swelling studies are conducted with in a cell containing artificial tear fluid, equipped with thermo jacket which maintains a constant temperature. Swelling medium equilibrating at 37°C 1 ml of formulated preparation is put in dialysis bag & placed into the swelling medium. At specific time interval the dialysis bag is removed from the swelling medium & record the weight. The swelling of the polymer which present in gel as a function of time is determined by following relationship.

$$\% St = (Wt - W0) 100/W0$$

Where,

St = Swelling at time 't'.

Wt=Final weight of gel.

W0=Initial weight of gelling solution.

8. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY^[2]

The high performance liquid chromatography is used in reversed phase mode. Analysis is performed by using a Nova pack C18 packed column (150 mm length X 3.9 mm i.d).

9. FOURIER TRANSFORMER INFRA RED (FTIR)^[2]

FTIR studies are done to investigate the possibility of drug-excipient interaction. Here FTIR graph of pure drug & mixture of drug and excipients are recorded by using KBR pellets. If both graphs are similar, means there is no interactions between drug and excipients.

10. THERMAL ANALYSIS^[2]

Thermo gravimetric analysis can be conducted for in situ gel forming polymeric system to determine the percentage of water content in hydrogel. Different scanning calorimeter is used in thermal analysis. As compare to pure ingredient if thermo gram shows many changes, indicates the interactions are taking place.

11. IN VITRO DRUG RELEASE STUDIES^[2]

Franz diffusion cell is used to study the *In vitro* drug release of in situ gel solution. Diffusion cell having a donor and a receptor compartment in which in receptor compartment freshly prepared simulated tear fluid and in donor compartment the formulation solution is placed. Dialysis membrane (0.22 µm pore size) is placed between donor and receptor compartment. The whole assembly is placed on magnetic stirrer which is thermostatically controlled. The medium temperature is maintained at 37.0°C ± 0.5°C. At specific time interval of 1 hour for 6 hour, 1ml sample is withdrawn and the sample volume is replaced with fresh medium (1ml). The withdrawn sample is transfer in 10 ml volumetric flask and makes up the volume up to 10 ml with solvent & analyzed by using UV spectrophotometer at respective wavelength. An equation generated from the standard calibration curve the drug content and the percentage cumulative drug release (% CDR) can be calculated. Further the obtained data is subjected to curve fitting for drug release data. The best fitting model is then checked for Krosmeysers peppas & Fickinian diffusion mechanism for their kinetics.

12. OCULAR IRRITANCY STUDIES^[2]

For these studies generally male albino rabbits, having weight around 1-2 kg are selected. The modified Draize technique is used to determine ocular irritation potential of ophthalmic preparation. The in-situ gel preparation is incorporated in lower cul-de-sac & at time interval of 1hr, 2hrs, 48hrs, 72hrs, & 1 week after drug administration irritancy will be tested. The albino rabbits are observed for swelling, redness & watering of eyes periodically.

13. ANTIMICROBIAL ACTIVITY

Antimicrobial efficacy studies are carried out to access the biological activity of *In situ* gel system against microorganisms. This is determined in nutrient agar medium by using 'Cup Plate method'.^[2]

The microbiological growth of bacteria is calculated by concentration of antibiotics and this has to be compared with that produced by standard antibiotic preparation

with known concentration. Serial dilution method is employed to carryout microbiological assay.^[1,5]

14. STERILITY TESTING^[2]

This test is carried out as per the IP 1996. The formulation is incubated in incubator for not less than 14 days at temperature 30⁰-35⁰ c in the thioglycolate medium to find out bacterial growth and & at temperature 20⁰-25⁰ c in Soya bean casein digest medium to find the growth of fungi in ocular preparation.

15. ACCELARATED STABILITY STUDIES^[2]

Formulation is placed in amber coloured vials & sealed with aluminium foil at temperature 40± 20 c & 75 ±5% RH as per the State Guidelines of International Conference of Harmonization (ICH). At every month sample is analyzed for clarity, drug content, pH, in vitro dissolution, gelling capacity, rheological evaluation.

CONCLUSION

From whole study it can be concluded that ophthalmic drug delivery system offers the novel carrier system for many pharmaceuticals. Ocular *In situ* drug delivery system offers more effective and protective means of the therapy for the nearly inaccessible diseases or syndromes of eyes. Polymers play an important role in the prolonged delivery of drug from its dosage form. Natural, synthetic and semi synthetic polymers are used to develop sustained release drug delivery system. The primary requirement of a successful controlled release product, concentrate on enhancing patient compliance which the in-situ gel offers. *In situ* gel is very reliable because it provides sustained and prolonged release of drug, good stability and biocompatibility. In recent technology, polymers combinations focus the development of safe ocular drug delivery system.

ACKNOWLEDGMENTS

The authors would like to thanks a lot to our honourable Mr. Asish Dev sir, oriental college of pharmacy, Tal. Navi Mumbai, Dist. Maharashtra, INDIA for their valuable comments and guidance. And spatial thanks to Mr. Yogesh Kate who supports me everytime.

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