# A Comprehensive Review On In Situ Ocular Gel

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## ABSTRACT

Eye is one of the most delicate part of body .Formulation and designing of the ophthalmic preparation is the most challenging field, reason behind this is that very less amount of drug entre in eye due to that it show less therapeutic effect and bioavailability .There are no of ophthalmic solutions in market, for the diseases of the eye and have many drawback too. To overcome this problem novel drug delivery is result to over the conventional drug. It shows better result better compliance better therapeutic effect and great residence time. An ocular in situ gel drug delivery is major focus. That these formulations are in solutions form but when this formulation change comes in contact with eye into gel form under physicochemical condition. In this review it covers the information about the gel, polymer used and approaches.

Keywords: ophthalmic, *insitu* gel, polymer.

### 1. Introduction

The eye is the mostly approachable for administration of medicament topical. Instillation of drug is major complication in ocular delivery (Aldrich et al., 2013). It is due the protective mechanism of the eye as well as nasolacrimal drainage, tear drain out blood barriers and endothelium and blood barrier present in the structure of eye, eye formulations cannot remain in the eye for the longer period and can't show its proper effect. (Wei et al., 2002) Main drawback of the formulation is that they drain out from the eye because they are in solution form.(Poland & Kaufman, 1988) Due to this the contact time and residence time decreases(Sawusch et al., 1988). customary ocular deliveries is suspensions, ointments, solution, are the fail to increase the contact time which results in low bioavailability(V. H. L. Lee & Robinson, 1986). substitution of the formulations to increase the result and get most effective result like collagen shields nanocarriers , (PUNCH et al., 1987)microspheres(Chak et al., 2013), penetration enhancer ,Ocuserts(Anumolu et al., 2010) . Novel approach effective formulation which increases the residence time and therapeutic effect of dosage form(Gaudana et al., 2010). Ph, ion sensitive, thermosenstive these factor gels are depended. In new approaches polymer play a very important role(Wang et al., 2008)(Van Der Bijl et al., 2001). Polymers are in solutions form before administration

but when they come in contact with body temperature they converted in to gel and in resultant the drug residence time increase which give better therapeutic effect.(Burgalassi et al., 2001)

**1.2 DISEASES OF EYE**

Glaucoma

Cataract

Conjunctivitis

Diabetic retinopathy

Retinitis pigmentosa

Pterygium

Ocular surface neoplasia (Patel Vishal & Institute, 2011)

## Glaucoma

Glaucoma involves great failure (RGC) retinal ganglion cells greater changes in the optic nerve which have greater loss in the vision of the eye(McMonnies, 2017).. Developing glaucoma is not that much risky but not detecting is the main problem loss of vision is the main problem (Quigley & Broman, 2006)

## Epidemiology

As per report worldwide estimated 57.5 million people are glaucoma affected, as per dat ain Europe 7.8 million people, and the most common in UK 2% older than 40 yr and 10 % older than 75 % and similarly in Nigeria about age of above 40 yrs patient. In India there are 30 million people are affected with this diseases. And 90% not recover with it and lost their vision.(Venkatesh, 2013)

**Cataract**

Cataract is condition where blurry vision in the lens due to the cloudy area. It happens when the protein in the eye forms a clumps and retina does not get form images.

## Epidemiology

Studies shows that blindness is due to cataract in world wide it went from 12.3million in 1990to 20 million in 2010 in South East Asia 12 % North America 42%, Latin America there is about 0.5%.(C. M. Lee & Afshari, 2017) In India 2001 there were 7.75 million who are suffering from cataract it is increased 8.25 in 2020 and mostly this is seen more commonly in age above 70 yr. It was estimated that

the number of cataract blinds per million people 50 years of age and older will drop from 53000by 30088 million by 2020 where cases are rampant blindness is considered .(Murthy et al., 2008)

## Conjunctivitis

Inflammation and conjunctiva or conjunctivitis. It mainly concerns the conjunctiva. It might be non-infectious or infectious .Allergic, toxic, irritation in the eyes are the non-infectious types..

## Epidemiology

It was seen that at 2015 half of the population at Europe was affected by conjunctivitis and in recent survey n united states 2765 which are maximum 5yrs older are with allergic , and conjunction of nose 39% , 34 % itchy eyes . 670242 children with age between 13 -14 across the 97 countries are affected by this problem. In India 68% infection on both the eyes it is most properly found in male as compare to female (Leonardi et al., 2015)

### Diabetic retinopathy

Diabetic retinopathy is disease cause by diabetes, too much sugar in the blood over time can damage blood vessel of whole body and retina too. Bleeding of the eye causes when sugar blocks the little blood vessel of the retina.

## Epidemiology

As per PRISM guide line studies from 2008 to 2018 it is increased .since 1980 that it is 110% in men and 58% in women and 7.9% worldwide, as per studie 422 million and future to be 622 million by 2045. (Cheloni et al., 2019)In India this study population came from Indian nationality from various regions of India, presented at these institutions in 2008 and there was a long-term follow-up of up to 10 years included in the study.(Cheloni et al., 2019)

### Retinitis pigmentosa

Retinitis pigmentosa is genetic disorder. This diseases cause breakdown of the cells in the retina, difficulties in seeing at night is the major cause loss and loss of vision.

## Epidemiology

It is estimated that 1 in 3500 are affected by this disease. In USD133.82million in 2017 cases are there. In EU 20.9 million 2018 and 21.33 million was seen in 20119 survey. In India 1:750 in more in adult population seen this problem.

**Ocular surface neoplasia**

In neoplasia spectrum of neoplastic changes squamous epithelium of the conjunctiva and cornea , it typically present fleshy conjuctival lesion with papillary and leukoplakic, and gelatinous appearance.(Ambulatory & Care, 2010)

## Epidemiology

It is most common seen in at the age of 55 -60, the age of the chart review cases was 73.2%Years with OSSN available at age 69.1%9.2 years. In India during studie in south India 95% patient are suffering from fundus in both the eyes. In urban population 1 in 930 and 1 in 372. (Quigley & Broman, 2006)

**2.MARKETED FORMULATION OF OPTHLAMIC SOLOUTION** (Jaswal et al., 2016)

| BRAND | DRUG | DOSAGE FORM | USE | DRAWBACKS |
|---|---|---|---|---|
| Ciplox | Ciprofloxin | Eye drops | Conjunctivitis and eye infection | Eye itching , tearing , low residence time |
| Acivir eye | Acyclovir | Ointment | Eye infection | Itching , change eye vision if use longer period of time |
| Ocupol | Polymixin -B | Ointment and eye drops | Corneal ulcer, bacterial infection | Irritation , stinging sensation ,blurred vision |
| Pred forte | Prednisolone acetate | Suspension | Anti inflammatory and anti allergic | Cloudy in under the lens |
| Chloromythecin | Chlorampthenicol palminate | ointment | Conjunctivitis and eye infection | Not confortable cloudy appearance after use . |
| Dexin | Dexamethasone | Eye drop | In eye infection | Low residence time due to drain out of |

| | | | | |
|---|---|---|---|---|
| | | | | solution |

## 3. DEMERIT OF OPTHALMIC SOLOUTION

- The site of action preservation of the drug is poor due to lower volume of tear. Applied does get out from the eye due to blinking or lachrymal duct.
- Blurring of vision temporary due to applying the ointment.
- Less therapeutic effect reason less residence time.
- Low corneal permeability
- Regular instillation (Baranowski et al., 2014)

## 4. NOVEL AND CURRENT APPROCHES

**COLLOIDAL SYSTEM**

**MICROEMULSION**

**NANOSUSPENSION**

**LIPOSOMES**

**DENDIMERS**

**HYDROGELS**

**MARKTED PRODUCTS OF NOVEL APPROCHES**.(Ramesh et al., 2017)

| **BRAND** | **DRUG** | **DOSAGE FORM** | **USE** |
|---|---|---|---|
| Cipla | Acilovir | Ointment | Anti-infective |
| Alcon laboratories | Diffluprednate | Emulsion | Anti inflammatory corticosteroid |
| Allergen | Dexamethasone | Implant | Macular edema |
| Aton pharma | Hydroxyl methlycellose | Insert | Lubricant and ophthalmic proctectant |

**ROUTES OF OCULAR DEIVERY**

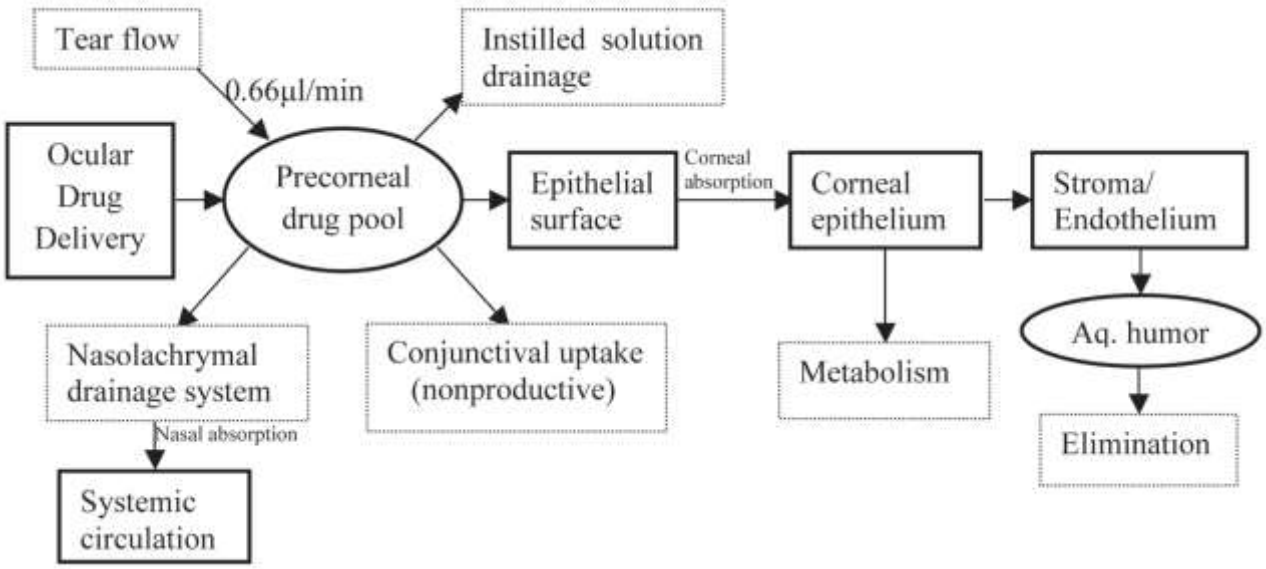



Fig 1: Representation of drug dispositioning intraocular and precorneal (Mundada & Avari, 2009)

Topical applied drug reaches to inner part of the eye to show the reaction, conversely due to tear drainage it can't reach. And decrease the concentration of the drug when the formulation which are in solution form administered in the form of drops cornea absorption is also very slow than elimation. Transcorneal penetration is the major route of drug absorption. Tight junction of the superficial facial conjunctiva epithelium is main barriers. (Kushwaha et al., 2012)

***Composition of the eye***

Water: 98%

NACL: 0.66%

Sugar: 0.65%

Organic element – protein: 0.67 %

Solid: 1.8%

**7. Mechanism of corneal absorption**

Cornea is the major route from where most of the drug entre to eye .conjunctiva and sclera are connect to the cornea and called non- corneal route .poorly absorbed drugs are absorbed by this route also having 5000 Daltons molecular weight pass through non corneal route.

**Corneal permeation route**

The penetration of drugs crossways the corneal membrane occurs from the precorneal gap. With the pore size 60a can pass through it a small ionic and lipophllic molecules. (Arul Kumaran et al., 2010) (Shelley et al., 2018)

## 8. IN SITU OCULAR GEL

In situ ocular gel are the delivery of ocular delivery follow the principle *sol to gel* basically this system convert the solution in to the gel when come me in contact with body temperature or eye in the cul de sac of the eye (Kavitha et al., 2013) under the suitable condition where they change the state ( ph , ion activated , thermosentive ) .(Nanjwade et al., 2009) polymers play an important role in situ formulation that it hold the drug and increase residence time. This also put good affect on bioavailability.(H. Gupta et al., 2010)

Universally more great than insoluble or soluble inserts with low viscosity are poor compared to other structural solutions — such as lubricants to increase the availability of bioavailability due to premature residence time. Decreased nasolacrimal duct drug The potential for unwanted side effects arising from systemic absorption of the drug through the nasolacrimal duct is also reduced when the drug is instilled in the eye not repeatedly used.(Kapoor, 2019)

**Merit OF IN SITU OCULAR**

- Blur vision is less as match up to ointments
- Patient compliance and comfort
- Prolong release and increases residence time and control release which maintains constant plasma time.
- Nasolacrimal drainage is less.
- Lower investment and manufacturing cost production is less complex..

## 9. THREE APPROCHES

THERMOSENSTIVE METHOD (TEMPERATURE INDUCED)

PH TRIGGERED METHOD

ION ACTIVATED METHOD

**THEMOSENSTIVE METHOD**

This method is mostly used in the formulation in this system formulation is in the form of solutions in the low the temperature but when the temperature is increased and come in contact with the human eye it change to sol to gel .at temperature (37 degree). These are the free flowing liquids, at room

temperature .There is gradually change in the polymer and get aggregate (form great network of the polymer). The conversion of the phase should be above room temperature. (W. Ma et al., 2008)

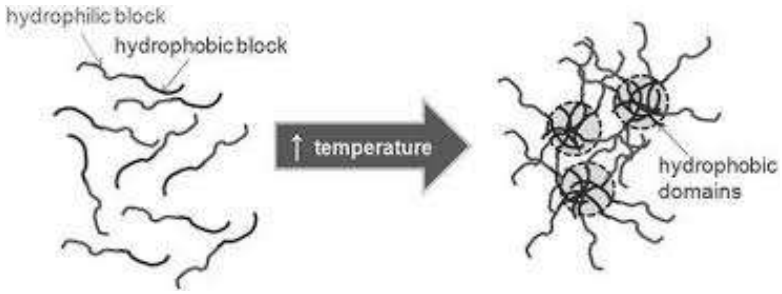
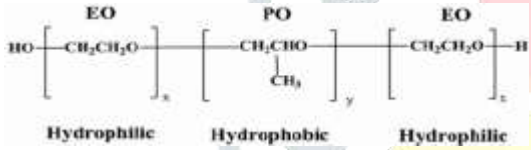



Fig. 2 Thermo sensitive (mechanism of phase transition in temperature) (Ramesh et al., 2017)

**Polymer used in Thermosenstive method:**

- Poloxmer
- Chitosan
- Sodium alginate (Lin & Sung, 2000)

**POLOXMER**




Poloxmer also known as pluronics , are non ion surfactants poloxmer is a water soluble tri-block copolymer incorporate of two polypropylene oxide (PPO) and polyethylene oxide (PEO) and interior in an ABA construction. (Ludwig, 2005)

PPO is hydrophobic and both side of it is surrounded by hydrophilic PEO .Poloxmer improve residence time with good thermosetting property. Concentrated pluronics Give reversible thermoreverssible gel. It depend on mechanism that on room temperature it is viscous bt when the temperature is increased than it turns into gel(Ludwig, 2005).

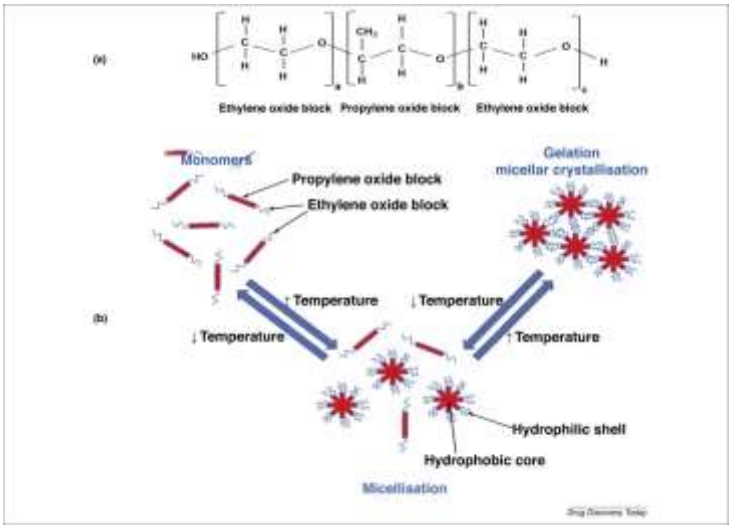
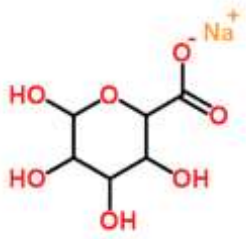



Fig 3 (a) poloxmer formulation in sol form (b) turn into gel form by increasing temp. (Soliman et al., 2019)

**SODIUM ALGINATE**

Sodium alginate is an ion-sensitive polymer. It is also known as sodium salts acid, lgenic acid, E401, sodium polymannuronate, Keltone, Kelcosol, Keltone.(S et al., 2017)




Sodium alginate structure

It is extract of brown algae .sodium alginate is salt of alginic acid. It is non toxic in nature . It has high molecular weight. Due to carboxylic acid it is having good mucoadhesive property. It is used as thinking and suspending agent. (Rowe et al., n.d.)

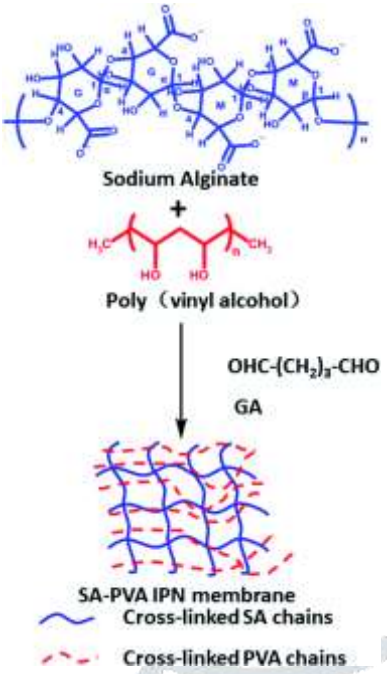
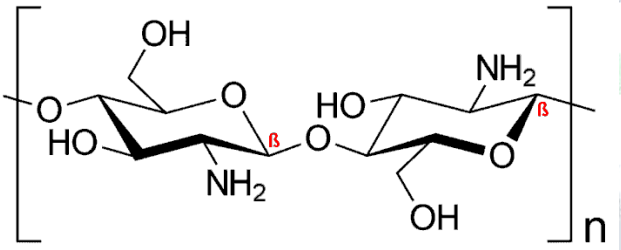



Fig 4mechanism of action sodium alginate 44

**CHITOSAN**

Chitosan is a polymer used as an excipient for delivering a variety of therapeutic properties the properties of nanotech. Gene therapy and targeting of drug, (Zou et al., 2020) Applications in drug administration, nanotechnology, delivery terms, or genetic therapy. It is a Natural Polymer obtains by deactivation of chitin. Chitosan turn into gel under the physicochemical condition . (Sa, 2003)




Structure of chitosan

Ionic interaction of chitosan is due to its mucoadesive property Chitosan is due to the formation of ionic interactions between well-charged amino groups and poorly charged sialic acid. It is used as a viscosity enhancer.(Sa, 2003)

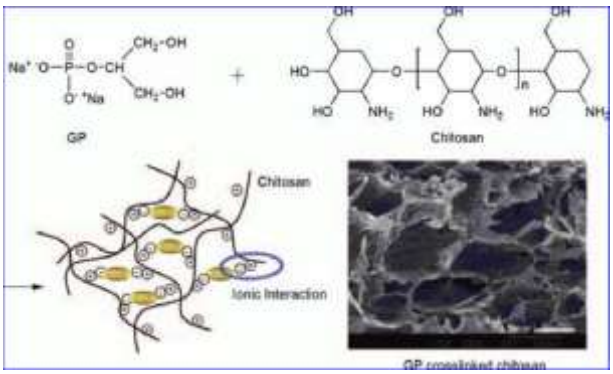



Fig 5 Formation to chitosan gel (Ahn et al., 2008)

**PH TRIGGERED METHOD**

PH induces systems in situ gelling solutions, which when touched the pH of the tear fluid transforms the gel phase. This is a polymer method with a weak acid or a weak foundation. This acquisition of a free proton receptor ..(W. Ma et al., 2008)

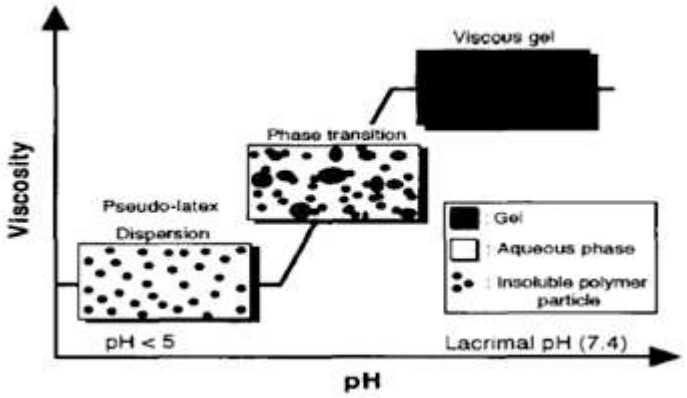
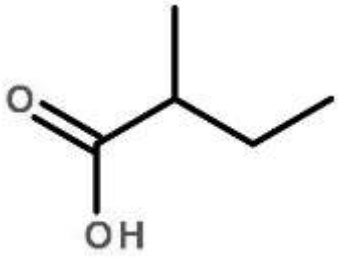



FIG 6. Ph change (Phase transition when polymer solution is in low ph than it is in sol. form when it change its ph it become viscous (Article, 2016)

## POLOYMER USED IN PH TRIGGERED METHOD

**Carbopol**

PAA polyacrylicacid is Carbopol. Sol to gel transition is shown by Carbopol, transition is shown by when the ph is changed or raised above its form 4 to 7. Carbopol remains sol. When it is in acidic but changes into low viscosity gel al low alkaline ph Carbopol viscosity is enhanced when it is used with hpmc and low the viscosity of the solution Carbopol (934,940, 941) Carbopol 940 show the best and better result than other grade (Vartak et al., 2018) [55]




Carbopol 934

**ION TRIGGERED METHOD**

In this method viscosity of solution is increased when the formulation come in contact with tear fluid polymer which are ion sensitive they are able to cross linked with standard tear fluid ion present in that resultant it increase the retention time .

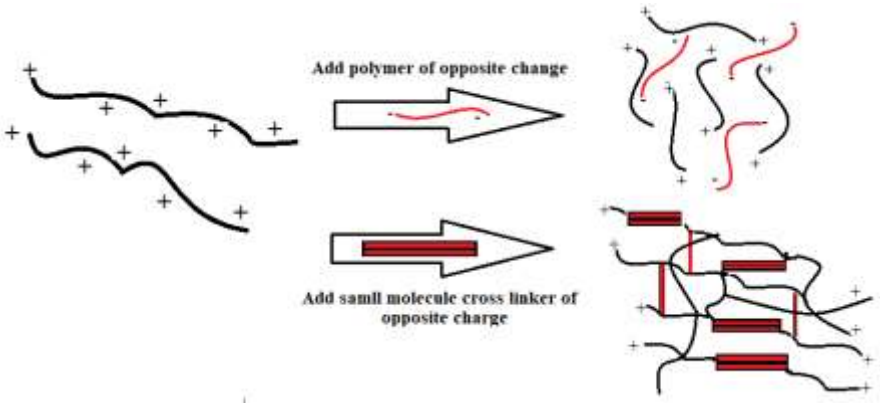
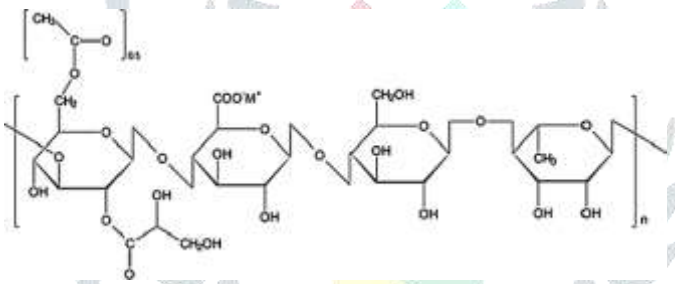



Fig 6 Ion activated system mechanism

**Polymer used in ion activated system**

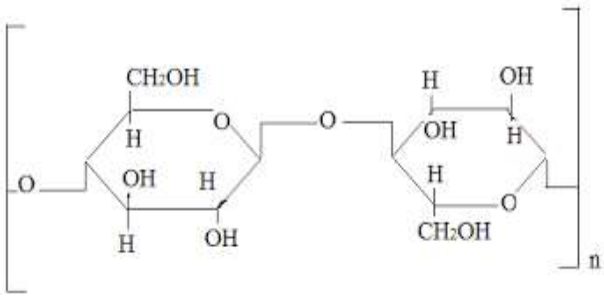
**GELLAN GUM**

Gellan gum is produced by the bacterium *Sphingomonas elodea* it is used as gelling agent polymer chain having glucose , gluronic acid ,rhamnose these unit are linked together to give a tetrasacchride. Removing the acetyl group from the gelrite molecule is deactivated gellan gum it is obtained by treating gellan gum with alkali.



**HPMC (hydroxyl propyl methyl cellulose)**

Hpmc is also known as methocel and Hyperomellose viscosity is increased by increasing the temperature (Rowe et al., n.d.)



Structure of hpmc

## Review of Literature

| Name OF DRUG | POLYMER USED | METHOD | RESEARCH OUTCOMES | REFERENCES |
|---|---|---|---|---|
| Pilocarpine hydrochloride | Pluronic F127, xyloglucan | Thermosentive method | The formulation containing xyloglucan (2.0% w/w) and 25% w/w Pluronic F127. This was the best formulation. | (Miyazaki et al., 2001) |
| Ciprofloxacin | Poloxamer , chitosan | Thermo sensitive method | This formulation containing Poloxmer 25%chitoson 3%. This was the best formulation | .(Varshosaz et al., 2008) |
| Moxifloxacin hydrochloride | Sodium alginate , hpmc 50 cps. | Ion activated | This formulation containing sodium alginate 1.500 g, hpmc 1,500g, drug 500mg. This was the best formulation | (Mali & Hajare, 2010) |
| Timolol maleate | Chitosan , gellan gum | ph triggered method , ion activated method | This formulation containing, chitosan 0.25%w/v, gellan gum 0.5%w/v. This was the best formulation | (H. Gupta et al., 2010) |
| Ketotifen fumarate | Gellan gum, cabopol.sodium Alginate | ph triggered method | This formulation containing Gellan gum -0.6 %, sodium alginate 0.8%.This was the best formulation | (Jaya Raja Kumar & Muralidharan, 2012 |
| Flucanazole | Carbopol934 | ph triggered | This formulation | Pathak et al., |

| | | | | |
|---|---|---|---|---|
| | | method | containing Surfactant 20.25% cabopol0.05 w/v% This was the best formulation | 2013) |
| Levofloxacin | Sodium alginate , chitosan | Ion activated | This formulation containing 0.5% sodium alginate, chitosan 0.2%. This was the best formulation | H. Gupta et al., 2015 |
| Levofloxacin | Hpmc E-15, sodium alginate | ph triggered method | This formulation containing, sodium alginate 0.2%, chitosan0.5%. was the best formulation | H. Gupta et al., 2015) |
| Loteprednol etabonate | Tween 80 ,transcutol | Emulsification method | This formulation containing 1.76wt% of capryol , tween 80 This was the best formulation | (Patel, Nakrani, et al., 2016) |
| Dexamethsone sodium phosphate ,torbymycin sulphate | Hpmc, Poloxmer 407. | Thermosenstive method | This formulation containing Hpmc 0.4%, P- 407-15.17%. This was the best formulation | (Patel, Thakkar, et al., 2016) |
| Ciprofloxacin Hydrochloride | HPMC, Pluronic F 127 | ph triggered method | This formulation containing Gelrite 0.6%,benzonium chloride 0.02,ciprofloxin This was the best formulation | (Kurniawansyah et al., 2018) |
| Besifloxin | Xanthum gum ,sodium alginate ,ethyl cellulose | ph triggered method | This formulation containing Sodium alginate 1200mg, xanthum gum- | (Kala et al., 2018) |

| | | | | |
|---|---|---|---|---|
| | | | 600mg. This was the best formulation | |
| Disulfiram | Pluronic (407,188) | Thermosenstive method | This formulation containing Pluronic 407 – 17%, Pluronic 188- 16%. This was the best formulation | (Zhang et al., 2018) |
| Nepfenac | HPMC , Sodium alginate | Ion activated method | This formulation containing Hpmc k4m 0.5%, sodium alginate 0.5%. This was the best formulation | (Shelley et al., 2018) |
| Ciprofloxacin Hydrochloride | HPMC, Pluronic F 127 | ph triggered method | This formulation containing Gelrite 0.6%,benzonium chloride 0.02, This was the best formulation | (Kurniawansyah et al., 2018) |
| Moxifloxacin hydrochloride | PluronicF127,gellangum,Carbopol | Thermosestive method | This formulation containing Pluronic (5.75% w/v), gellan-gum (0.16% w/v), carbopol (0.15% w/v) This was the best formulation | C. Gupta et al., 2019) |
| Voriconazole | Pluronic (118,407), Carboxy methly cellulose | Thermosentive method | This formulation containing In g P-407-(15), P-188-(25),cmc-0.3 FOR 100ML This was the best formulation | (Üstündağ Okur et al., 2019) |
| Moxifloxin HCL | Termanlia arjuna , Sodium alginate | pH triggered method | This formulation containing All ingredients is in w/v. | (Noreen et al., 2020) |

| | | | | |
|---|---|---|---|---|
| | | | P- 5.75%, carbopol (0.15%), gellan gum (0.16). This was the best formulation | |
| Curcumin | Cholesterol, Tween 80 | Lyophilisation method | These formulations containing Cholesterol 5%, tween 2ml. This was the best formulation | (Aboali et al., 2020) |
| Vinpocitine | HPMC, Carbopol 940 | ph triggered method | This formulation containing Carbopol - 0.4 %, hpmc 1.5% This was the best formulation | (Q. Ma et al., 2020) |
| Tetrahydrolozine | Poloxamer 408,118 | Thermosentive method | This formulation containing Formulation code TI-3 ,P18815%w/w, P40720%, drug 0.05g and benzonium chloride 0.002. This was the best formulation | (Okur et al., 2020) |
| Acyclovir | Pluronic(407,188) | Thermosentive method | This formulation containing P(407) 15%,P(188 ) 20% This was the best formulation | (Mahboobian et al., 2020) |
| chloramphenicole | Hpmc, Poloxamer 407 | Thermosentive method | This formulation containing Hpmc1.0%w/w) and 26% w/w poloxamer 407 This was the best formulation | (Kurniawansyah et al., 2020) |
| Tauroursodeoxycholic acid (TUDCA | Carbopol , Hpmc | ph sensitive method | This formulation containing Cabool 974 - 0.30%, hpmc | (Ni et al., 2020) |

| | | | | |
|---|---|---|---|---|
| | | | 0.47%ethyl parben 0.06%. This was the best formulation. | |

**PATENT**

Over the past few decades, a large number of studies were done in *in situ gel* system. Some of them mention below.

| **PUBLICATION** | **DATE OF PUBLICATION** | **FORMULATION** | **METHOD** | **REFERENCES** |
|---|---|---|---|---|
| In vitro and in vivo evaluation of Gelrite® gellan gum-based ocular delivery system for indomethacin | 2003 | Gellan gum was dissolved in hot phosphate having ph 7.4 with portion add sodium citrate with continue stirring at 40 °C.finally add drug and autoclave it | Ph triggered | (Balasubramania |

| | | | | |
|---|---|---|---|---|
| Study of an alginate/HPMC-based in situ gelling ophthalmic delivery system for gatifloxacin | 2006 | The alginate soloution were prepared adding alginate in 75 ml of solution the hpmc in desired concentration with continue stirring. add drug in final concentration | Ion sensitive method | (Liu et al., 2006) |
| Carbopol/chitosan based pH triggered in situ gelling system for ocular delivery of timolol maleate | 2010 | Chitosan was dissolved in acetate buffer of ph 4.6 at concentration of 0.5%w/v preparations of carpool solution in finally add drug | Ph triggered | (S. Gupta & Vyas, 2010) |
| Development and characterization of in-situ gel for ophthalmic formulation containing ciprofloxacin hydrochloride | 2016 | Chitosan is dissolved in 0.1 M acetic acid glycerol 2 phosphate disodium salt phosphate salt hydrate solution filtration and sterilization add drug in final preparation | Ph triggered method | (Makwana et al., |
| Thermo sensitive chitosan-based hydrogen as a topical ocular drug delivery system of latanoprost for glaucoma | 2016 | Chitosan is dissolved in 0.1 M acetic acid glycerol 2 phosphate disodium salt phosphate salt hydrate solution filtration and sterilization add drug in final preparation | Thermosensive method | (Gadad et al., |

## Conclusion

Ophthalmic drug delivery is increasing rapidly and most challenging field. Novel drug delivery is the best result in the recent years and which is very important for the ophthalmic system. And the result

shows that better patient compliance and comfortable. It overcomes the problems related to ophthalmic solutions by increasing residence time and therapeutic effect. Biodegradable polymer is used in this system which decreases the toxicity. For better result and advancement nonocarries are also incorporated in this system.

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