Review Article

Polymers Used in Ophthalmic *in Situ* Gelling System

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ABSTRACT

Eye is a sensitive organ and is easily injured and infected. Delivery of drugs into eye is complicated due to removal mechanism of precorneal area results decrease in therapeutic response. Conventional ocular delivery systems like solution, suspension, ointment shows some disadvantages such as rapid corneal elimination, repeated instillation of drug and short duration of action. *In situ* polymeric delivery system will help to achieve optimal concentration of drug at the target site, thereby helps to attain the desired therapeutic concentration. *In situ* gelling systems are liquid upon instillation and undergo a phase transition to form gel due to temperature modulation, change in pH and presence of ions. This review stresses the role of stimuli-responsive polymers in ocular *in situ* gelling system for prolonged contact time of drug with cornea, delay elimination and enhance bioavailability.

Keywords: *In situ* Gel, pH sensitive, Temperature sensitive, Sol-gel transition**.**

INTRODUCTION

Ophthalmic delivery system is a challenging area for the formulation chemist due to unique anatomy and physiology of the eye, which consists of three layers namely: Epithelium, Stroma and Endothelium. Outer epithelium layer act as barrier for hydrophilic drug, while stroma acts as diffusion barrier for lipophilic drug. Endothelium is lipoidal in nature[1, 2]. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. Topical drug delivery is a desirable route for drug administration. It will provide better relief, easy administration and improve patient compliance[2, 3]. Conventional dosage forms like eye drop, is commonly used but it has some disadvantages like rapid spillage of drug from eye results low therapeutic effect, repeated drug administration is needed. Repeated dose administration results damage to eye tissue. However viscous semisolid formulations like ointment and gel provide sustained release but it has some drawbacks like blurred vision, sticky sensation results eye irritation[3].

In ophthalmic drug delivery, a challenging task is normal ocular protective mechanisms like blinking, tears drainage; that promote rapid clearance, reduce bioavailability which results short duration of pharmaceutical response[4]. To increase corneal residence time and improve bioavailability, different ophthalmic delivery systems like gels, suspension, collagen shield and inserts are developed. Because of blurred vision, variability in dose instilled, sticking of eye lids and patient discomfort these formulations have not been widely accepted[5].

In recent years, there have been significant research efforts for the design of ophthalmic delivery system that are provided sustained and controlled drug release. *In situ* gelling system is such type of delivery system, where it is liquid upon instillation and undergoes phase transition to viscous gel in accordance with pH, temperature, electrolyte composition[6]. Compared to conventional formulations, *in situ* forming drug delivery system possesses some advantages which includes; ease of administration, simple manufacturing process and improved bioavailability. Therefore, this delivery system combines the advantages of both solution and gel such as ease of administration and prolonged the residence time. Thus, it provides improved patient compliance, reduce dosing frequency and increase bioavailability[7].

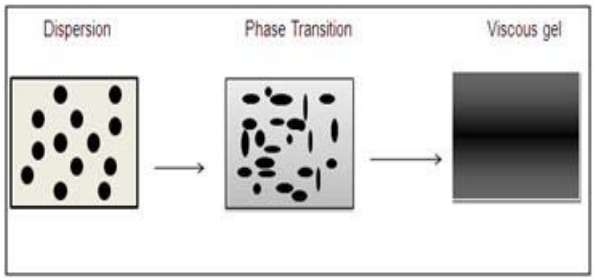


Figure 1: Mechanism of sol-gel transition

Ideal Characteristics of Polymers [8]:

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

Table 1: Polymers used for ocular *in situ* gelling system[9, 10]

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	Nonionic	Soluble	+
Xyloglucan	Natural	Anionic	Soluble	+
Poloxamer	Synthetic	Nonionic	Soluble	++
Sodium alginate	Natural	Anionic	Soluble	++
HPMC	Natural	Nonionic	Soluble	+
Mucoadhesive capacity : Excellent(+++), Good(++), Poor(+)				

Classification of *in situ gelling* system[11]

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

In this system, gelling of the solution is triggered by change in pH, when pH is raised from 5-7.4[12]. At higher pH, polymer forms hydrogen bond with mucin, which leads to hydrogel formation. Cellulose acetate phthalate latex, Carbopol, Polyacrylic Acid, Polyethylene Glycol are pH dependent polymers.

Mechanism for pH sensitive gelling System

All pH sensitive polymers contain pendant acidic or basic groups that can either accept or release protons in response to changes in environmental pH. In case of weakly acidic group, swelling of hydrogel increases as the external pH increases, while decreases in case of weakly basic groups [13].

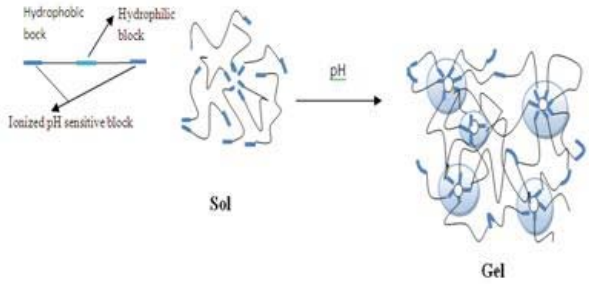


Figure 2: Mechanism of pH sensitive *in situ* gelling system[14]

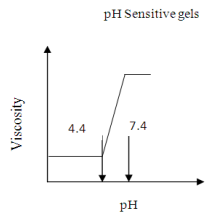
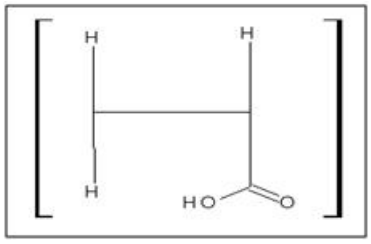


Figure 3: Graphical representation of pH sensitive *in situ* gelling system

Polymers used in pH sensitive *in situ* gelling system

- **Carbomer**



Scheme 1: Structure of Carbomer

Properties

Carbomer is a high molecular weight, cross linked polyacrylic acid derivative and has strongest mucoadhesive property. It is water soluble vinyl polymer. In aqueous solution, it shows sol to gel transition, when the pH is raised above its pKa of about 5.5[15]. As the concentration of carbomer increases, its acidic nature may cause irritation to eye. Addition of cellulose will reduce polymer concentration as well as will improve gelling property. Different grades of carbomer are available in market which includes carbopol 934(lowest cross linking density), carbopol 940 (highest cross linking density), and carbopol 981 (intermediate cross linking density). Carbopol is used as gelling, emulsifying and suspending agent[16].

Mechanism

Mucoadhesive property is due to hydrogen bonding, electrostatic interaction or hydrophobic interaction[17]. Carbopol molecule is tightly coiled acidic molecule. Once dispersed in water, carboxylic group of the molecule partially dissociates to form flexible coil. Being a pH sensitive polymer, increase in solution pH results swelling of polymer. In acidic medium, it is in collapsed state due to hydrogen bonding, as the pH increases, electrostatic repulsion occur between the anionic groups, results gel swelling[18]. The gelling effect is activated in two stages: Dispersion and hydration of carbopol, neutralizing the solution by addition of sodium hydroxide, Triethanolamine, or potassium hydroxide. As the concentration of carbopol increases, due to its acidic nature it causes irritation to the eye. Addition of viscosity enhancer like HPMC, MC will reduce the concentration without affecting its gelling property[17, 18].

Srividya *etal*., developed a pH triggered ophthalmic delivery of ofloxacin by using carbopol and HPMC, results indicated that it produce sustained release over a period of 8 hours [19].

Lin HR *et al*., formulated a carbopol/pluronic based ocular *in situ* gelling system. The mixture of 0.3% carbopol/14% pluronic solution showed significant enhancement in gel strength and bioavailability [20].

Pandey *et al.,* developed ocular *in situ* gel of levobunolol hydrochloride. The combination of mucoadhesive

carbopol and viscosity enhancer HPMC provide sustained action over a period of time [21].

Mohanambal *et al.,* developed carbpol/HPMC based pH triggered ocular *in situ* gel of levofloxacin. The developed formulation was stable, non irritant and sustained release over a period of time [22].

Polycarbophil[23]

Polycarbophil is lightly cross linked polyacrylic acid having excellent mucoadhesive property.

Mechanism

It is insoluble in water but its swelling capacity in neutral medium permits the entanglement of polymer chain with mucus layer. The carboxylic acid group of polycarbophil binds to mucin by hydrogen bonds. Noveon®AA-1 polycarbophil, is a high molecular weight polyacrylic acid polymer cross linked with divinyl glycol and exhibit sol-gel transition [23, 24].

Cellulose acetate latex (CAP latex) another pH sensitive Polymers these are flowing liquid at pH 4.8 and gel at pH 7.4.

2. Temperature sensitive *in situ* gelling system[25]

These are liquid solutions at room temperature (25-27°C) and undergo gelation when in contact with body fluid (35-37°C) due to change in temperature. Temperature sensitive gels are three types; positive temperature sensitive gel, negative temperature sensitive gel, thermally reversible gel. Negative temperature sensitive gel has Lower Critical Solution Temperature (LCST), such gel contracts on heating above LCST[25, 26]. Positive temperature sensitive gel has an Upper Critical Solution Temperature (UCST) such gel contracts on cooling below UCST.

Mechanism:

The sol-gel phase transition occurs upon increasing temperature is due to three mechanisms: Desolvation of the polymer, increased micellar aggregation and increased entanglement of polymeric network[27]. When temperature increases polymeric chain degraded, leads to the formation of hydrophobic domain and phase transition (liquid to hydrogel) occurred [28].

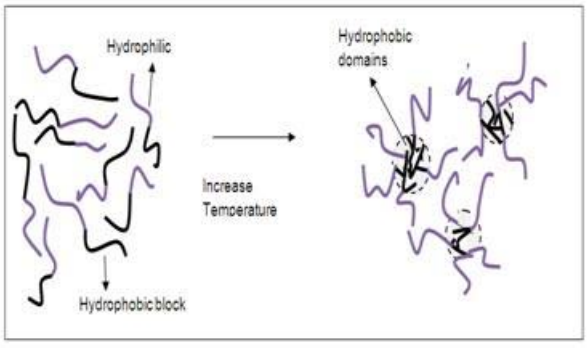


Figure 4: Mechanism of Temperature sensitive *in situ* gelling system [14]

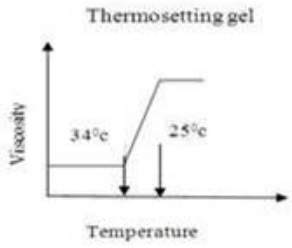
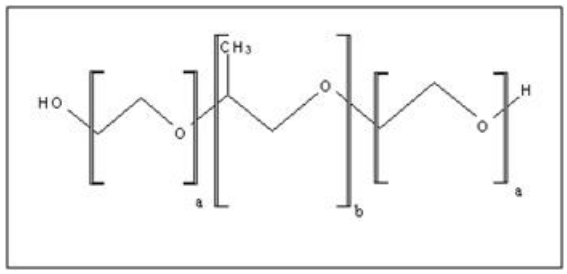


Figure 5: Graphical representation of temperature sensitive *in situ* gelling system

Polymers used in temperature sensitive gelling system

- **Poloxamer**



Scheme 2: Structure of Poloxamer

Poloxamer are water soluble tri-block copolymer consisting of two polyethylene oxide (PEO) and polypropylene oxide (PPO) core in an ABA configuration[29].

Properties

It is commercially available as Pluronic® and has good thermal setting property and increased drug residence time. It is used as gelling agent, emulsifying agent and solubilizing agent. Poloxamer gives colourless, transparent gel [30].

Depending upon the ratio and distribution of hydrophilic and hydrophobic chain several molecular weights available, having different gelling property[30].

Table 2: Classification of poloxamer

Poloxamer	Molecular Weight
124	2200
188	8400
237	7959
338	14600
407	12600

Mechanism of gelling action

It consists of central hydrophobic part (polypropylene oxide) surrounded by hydrophilic part (polyethylene oxide). At room temperature (25°C), it behaves as viscous liquid and is transformed to transparent gel when temperature increases (37°C) [31]. At low temperature, it forms small micellar subunit in solution and increase in temperature results increase in viscosity leads to swelling to form large micellar cross linked network [14].

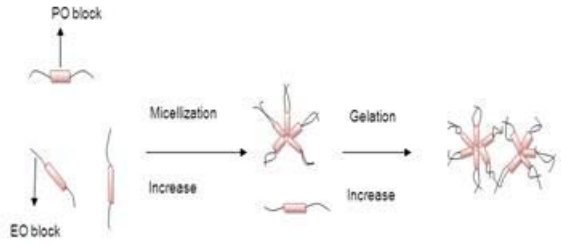


Figure 6: Gelling mechanism of Poloxamer[14]

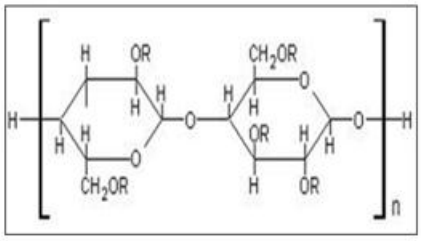
Kamel *et al*., developed a Pluronic F 127 based *in situ* gelling system containing timolol maleate for sustained ocular delivery. *In vivo* study showed that ocular bioavilability of Pluronic F127gel based formulation increased by 2.5 fold as compared with aqueous timolol solution [32].

Qui *et al*., developed a pluronic and carbopol based ocular *in situ* gelling containing puerarin. Incorporatoion of carbopol enhance mucoadhesive force and provide sustained drug release over a period of 8hrs [33].

Qian Y *et al*., formulated temperature sensitive poloxamer based *in situ* gelling system of methazolamide, for increasing corneal residence time and bioavilability. From the study, in vitro release shows that diffusion controlled release of drug from poloxamer solution over a period of 10 hours [34].

Cao F *et al*., developed poloxamer/carbopol based ophthalmic *in situ* gelling system of azithromycin. Addition of carbopol 974 could increase the solubility of azithromicin by salt effect and enhance mucoadhesive property. The formulation exhibited 24 hour sustained release [35].

- **Cellulose derivative**



Scheme 3: Structure of HPMC

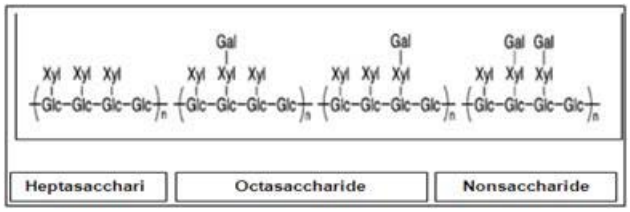
Cellulose is composed of glucan chain with repeating β-(1,4)-D-glucopyranose unit. Natural polymers like HPMC, MC, and EC exhibit temperature sensitive sol-gel phase transition[36]. Cellulose material will increases its viscosity when temperature is decreases while its derivatives like HPMC, MC, will increase its viscosity when temperature is increased [37].

MC is composed of native cellulose with alternate methyl substitution group on its chain. At low temperature (30°C) solution is in liquid form and when temperature is increases (40-50°C) gelation occurred.

Mechanism

Gelation of cellulose solution is caused by hydrophobic interactions between molecules containing methoxy substitution. At low temperature, molecules are hydrated and little polymer-polymer interaction occurs, whereas at high temperature, polymers lose their water of hydration[37].

- **Xyloglucan**



Scheme 4: Structure of Xyloglucan

Xyloglucan is water soluble hemicelluloses obtained from vascular plants and it exhibit thermally responsive behavior when more than 35% galactose residues are removed. It composed of (1,4)-β-D- glucan back bone chain(GLC) with (1,6)-α-D- xylose branches (XYL), partially substituted by (1-2)-β-D-galactoxylose (GAL) [37,38].

Properties

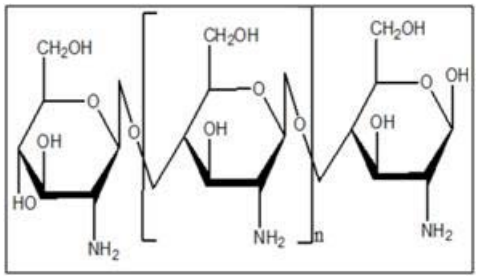
Xyloglucan is consists of three different oligomers like heptasaccharide, octasaccharide, nonsaccharide, which differ in number of galactose side chain. It is widely used in oral, rectal, ocular drug delivery due to its non- toxicity, biodegradable and biocompatible property. Like, poloxamer it exhibit gelation on heating refrigerator temperature or cooling from a higher temperature. But the difference is xyloglucan forms gel at lower concentration (1-2%wt) [39].

Mechanism

In native form of xyloglucan does not show gelation, its dilute solutions form so-gel transition on heating due to partial degradation of β-galactosidase. The transition temperature is inversely related to galactose removal ratio and polymer concentration [40].

Miyasaki S *et al*., developed xyloglucan based ocular in situ gelling system of pilocarpine. That results degree of enhancement of miotic response followed by sustained release of pilocarpine [41].

- **Chitosan**



Scheme 5: Structure of Chitosan

Chitosan is a cationic polysaccharide consisting copolymers of glucosamine and N-acetyl glucosamine, these are natural polymer obtained by deacetylation of chitin. Chitosan has mucoadhesive property due to electrostatic interactions between positively charged amino group and negatively charged mucin. It is non toxic, biocompatible, biodegradable polysaccharide and having bioadhesive, antibacterial activity [42].

Mechanism

The mucoadhesive property is due to the formation of ionic interaction between the positively charged amino groups of chitosan and negatively charged sialic acid residues of mucins, depends on environmental pH[43]. Because of its bioadhesive, hydrophilic, good spreading properties, is used as viscosifying agent in artificial tear formulations [44, 45].

Gupta H *etal*., was developed ion and pH sensitive *in situ* gelling system for sustained delivery of timolol maleate. Chitosan and gellan gum were used as gelling agent, it enhance transcorneal drug permeation [46].

Gratieri T *et al.,* developed chitosan/poloxamer based *in situ* gelling system. The results indicated that chitosan improves the mechanical strength of poloxamer and increase mucoadhesive activity [47].

Felt O *et al.,* developed chitosan based ophthalmic gel for enhancing corneal residence time when compared to tobrex® [48].

3. Ion Sensitive Gelling System

Gelation is triggered by the presence of cations (Na+, Mg++, Ca++) in the tear fluid. These can be achieved by polymers like sodium alginate, gellan gum [49].

Gelation is occurred by ionic interaction of polymer and divalent ions of tear fluid. When anionic polymers come in contact with cationic ions, it converts to form gel [50].

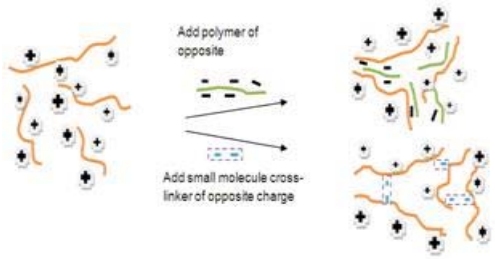


Figure 7: Mechanism of Ion sensitive *in situ* gelling system[14]

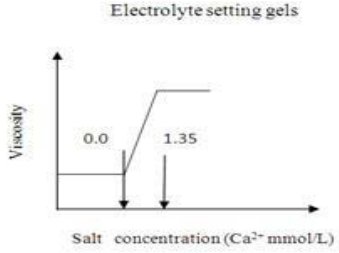
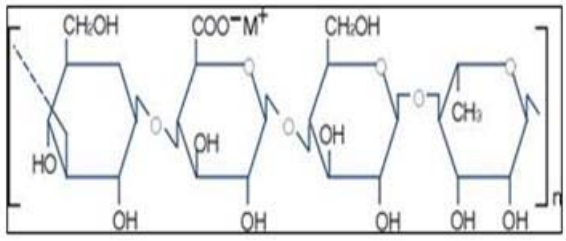


Figure 8: Graphical representation of ion activated *in situ* gelling system

Polymers used for ion sensitive *in situ* gelling system

- **Deacetylated gellan gum (Gelrite)**



Scheme 5: Structure of Gelrite

Gellan gum is an anionic hetero polysaccharide, secreted by microbe *Sphingomonas elodea*. It consists of glucose, rhamnose, glucuronic acid and are linked together to give a tetrasaccharide unit [51].

Properties

Gelrite is deacetylated gellan gum, obtained by treating gellan gum with alkali to remove the acetyl group in the molecule. Upon instillation, gelrite forms gel due to the presence of calcium ions[52]. The gelation involves the formation of double helical junction zones followed by aggregation of double helical segment to form three dimensional networks by complexaton with cations and hydrogen bonding with water[53]. Because of its thixotropy, thermo plasticity, pseudo plasticity are widely use in ophthalmology. In food industry, is used as suspending and stabilizing agent [23].

Mechanism

Gellan gum produce a cation induced *in situ* gelation (Ca^{2+}, Mg^{2+}, K^{+}, Na^{+}) due to the cross linking between negatively charged helices and mono or divalent cations (Na+, Ca+, Mg+). Divalent ions superior to promoting gelation as compared to monovalent cations. Gelation prolongs the residence time of drug at absorption site and bioavailability of the drug is increased [54].

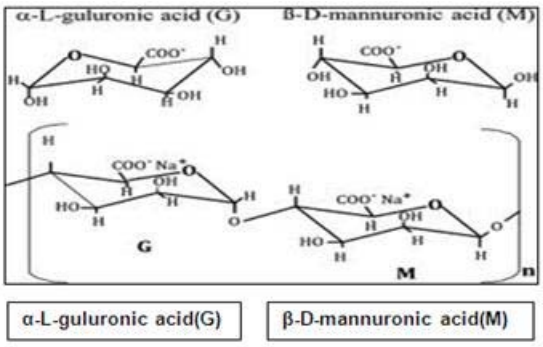
Vodithala S *et al.,* was developed gelrite based ion activated *in situ* gel of keterolac tromethamine and concluded that formulation produces sustained action over a period of 6 hours [55].

Geethalakshmi A *et al.,* developed gelrite based *in situ* gelling system of brimonidine tartarate and produce sustained release of drug [56].

Balasubramaniam J *et al.,* formulated gelrite based ion activated *in situ* gelling system of Indomethacine. Gelrite forms gels in the presence of mono or divalent cations present in the lacrimal fluid and it produce sustained release over a period of 8 hours [57].

Rajas N J *et al.,* developed gelrite based ocular *in situ* gel of levofloxacin hemihydrate for bacterial infections. The developed formulation shows better corneal residence time and sustained release of the drug [58].

- **Sodium Alginate**



Scheme 9: Structure of sodium alginate

Sodium alginate is a gum extracted from brown algae. It is a salt of alginic acid. It is a linear block polysaccharide consisting of two type monomers β –D- Mannuronic acid and α-L-glucuronic acid residues joined by 1,4 glycosidic linkages[59]. It exhibit good mucoadhesive property due to its carboxylic group. It is biodegradable and non toxic [60].

Mechanism

The monomers of alginate (β-D-mannuronic acid (M) and α-L- glucuronic acid (G) are arranged as M-M block or G-G block with alternating sequence (M-G) block. Upon interaction of G block of polymer with calcium moieties resulting in the formation of homogenous gel. Mechanical strength and porosity of hydrogel depends on G: M ratio, type of cross linker used and concentration of alginate solution [61, 62].

Liu Z *et al.,* developed ophthalmic gelling system of Gatifloxacin using alginate in combination with HPMC which acted as viscosity enhancing agent. Both in vitro release and in vivo corneal retention studies showed that HPMC/ alginate solution better retained than alginate/HPMC alone [63].

D.N Mishra *et al.,* designed *in situ* gelling ocular insert of gatifloxacin using sodium alginate and chitosan. In vitro release indicated that it provide sustained release over a period of 8-12 hours [64].

Abraham S *et al.,* developed Ofloxacin ion activated *in situ* gelling system using combination of polymers Alginate and HPC. Alginate/HPC solution retained the drug better than the alginate/HPC solution alone [65].

Preetha JP *et al.,* developed sodium alginate based diclofenac sodium *in situ* gelling system. The results indicated that sodium alginate/HEC solution shows better drug retained and antibacterial, antifungal, antimicrobial activity with selected micro organisms [66].

CONCLUSION

Polymers play a vital role in the delivery of drug from its dosage form. Polymeric *in situ* gelling system provides prolonged release of drug as compared to conventional delivery system. Various natural, synthetic, semi synthetic polymers are developed for controlled release of drug. Use of biodegradable and biocompatible polymers for *in situ* gel formulation makes acceptable and controlled drug delivery system. Thus sustained and prolonged release of drug, biocompatibility characteristics makes *in situ* gel dosage form reliable. In recent technology, polymer combinations focus the development of safe ophthalmic delivery system.

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