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## **BIODEGRADABLE POLYMERS USED IN OPHTHALMIC *IN SITU* GEL SYSTEM: A REVIEW**

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### **ABSTRACT**

Ophthalmic drug delivery system is one of the most challenging aspects with respect to drug delivery as human eye consists of tremendous barriers and this result into certain problems like low bioavailability which overall reduce the efficacy of the treatment. *In Situ* gelling system is considered as a unique method which is developed in order to increase the bioavailability of drug as well as to achieve a controlled manner of drug delivery. These are the gelling system which is liquid at room temperature but once, these are instilled into the human eye, they get modified into gels which involve different mechanisms like changes in temperature, pH or ionic environment. The present review focuses on the use of biodegradable polymers that are being

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employed in the formulation of this gelling system and their wide acceptability in designing of this system.

**Keywords: Ophthalmic, *In Situ* Gel, Natural Polymers, Bioavailability**

## INTRODUCTION

Ophthalmic drug delivery system is one of the most interesting field and many of the scientists and formulators all over the world remain focused in this branch. The conventional ocular drug dosage forms have proved to be lacking in many of the aspects in the past. They have a lesser bioavailability and the patient compliance is also minimal due to its frequent administration which makes them a poor choice when considering all of these aspects. Further, the anatomical construction of the human eye which bears many of the ocular barriers, make these dosage forms less therapeutically effective. To overcome all of these problems, Ophthalmic *In Situ* gelling system is being developed by using some different biodegradable polymers which remains in a liquid form but as these are instilled into the eye, these get modified into a gel form due to the presence of various physiological conditions like temperature, pH and the ionic environment. This definitely increase the residence time in the pre-corneal area and ultimately enhance the bioavailability of the drug. For designing such systems, a lot of different polymers have been employed in

the past but here the appreciation is being given to the biodegradable polymers which have some superior properties. Biodegradable polymers present great benefits in the clinical applications and approach. The formation of *In Situ* gelling system for ocular drug delivery is primarily associated with three main mechanisms which is appreciated below:

Temperature sensitive system: This type of formulation could be applied to the eye in liquid form and the gel is formed at the precorneal site at a temperature of 35° centigrade [1]. It is necessary here to illustrate that the gelation temperature of this type of formulation is quite higher than the normal room temperature and thus a transition from sol-gel is observed at the precorneal area due to this property [2].

pH sensitive system: Here the formulation is modified from a liquid to gel form due to the presence of change in the pH. The solution or liquid form is observed at a pH of 4.4 but when the formulation is administered into the eye, the liquid form gets converted into a viscous gel form because it is evident that in the precorneal area, the pH is changed to 7.4

which becomes a reason of sol-gel transformation [2].

Ionic triggered system: The lachrymal fluid in the eye has a significant ionic concentration due to the presence of cations in the monovalent and divalent forms and due to this aspect, the liquid form of the formulation is changed into the viscous gel

form. This system involves the use of some Ion-sensitive polymers which have an ability to form a cross linkage with the ions of tear fluid on the surface of eye which further results into an enhanced residential time of the drug on the ocular surface [3].

The three types of mechanisms could be depicted from the following table with its distinguishing features:

**Table 1: Types of *In-Situ* Gelling Systems & mechanisms involved**

Serial No	Types of <i>In-Situ</i> Gelling Systems	Mechanisms Involved
1	Temperature sensitive system	The liquid-gel transition takes place due to a change of temperature primarily at 35° centigrade.
2	pH sensitive system	The change in pH from 4.4 to 7.4 at the ocular surface results into a viscous gel formation.
3	Ionic triggered system	The presence of ionic concentration in the lachrymal fluid results in the formation of gel.

## BIODEGRADABLE POLYMERS USED FOR *IN SITU* GELLING SYSTEMS

### Classification of Polymers used for *In Situ* Gelling System:

Polymers are basically distinguished into two of the primary classes: [4, 5, 6]

**a. Natural polymers** – These are the polymers that are derived from the living sources like animals and plants and their quality is that they do not pose any harmful effect on the environment and living systems. The main examples of such polymers are Chitosan, Carbopol, Gellan Gum, Xyloglucan, Alginate Acid, Sodium Alginate, Pectin etc.

### b. Synthetic or semi-synthetic polymers-

They are manmade and totally prepared in the laboratory with the involvement of various chemical reactions. They have an attribute of modification according to the needs of drug delivery system and thus they have gained much importance in the past. Such polymers include some important examples like Poloxamers, Methyl Cellulose, Polyacrylic acid, Cellulose acetate phthalate, Poly ethylene glycol etc.

### Polymers used for Temperature Sensitive *In Situ* Gelling System:

**Poloxamer:** Poloxamers are also referred to as Pluronics and the mechanism involved behind them for causing *in situ* gelation is the

change in the temperature. These are generally the triblock copolymers which contain the poly (oxyethylene) and poly (oxypropylene) units. The changes associated with the sol-gel formation are due to the change in environmental temperature.

Pluronic™ F-127 is the commercially available product and it could be appreciated here that a 25-40% aqueous solution of this material will change the liquid form into a viscous gel when it comes in the contact of body temperature, and the release of drug from such a formulation can be extended till a period of seven days [7]. These polymers are readily available in different grades but these are distinguished from each and other from their molecular weight as well as the forms which are available physically. From the past data which is available of these polymers, an inference could be made that these are designated as three grades which are given an assignation of F which means

Flakes, P which is given to pastes and L is assigned for the Liquid polymers [8]. Amongst the different grades of Poloxamer polymers, the most versatile used grade is the Pluronic F127 which is widely accepted by the pharmaceutical companies because it has the attributes of generating transparent gels and without any color. The concentration of Poly ethylene oxide is 70% and the Poly propylene oxide is present in 30% concentration in this polymer. From the past, we could infer that for enhancing the ocular residence time and also to improve the bioavailability aspect, Pluronic F-127 g-poly acrylic acid is used as an important vehicle in the preparation of In Situ gels [9, 10, 11]. Another grade of Poloxamer is the Poloxamer 188 which is used in a combined form with Poloxamer 407 to optimize the range of gelation temperature and to further increase its acceptability in the production of Ocular dosage forms [12, 13].

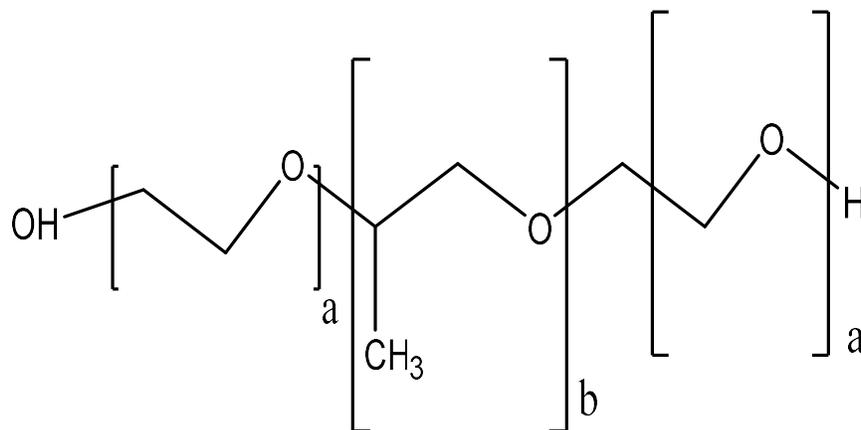


Figure 1: Depiction of Chemical Structure of Poloxamer-407 polymer

**Polymers Derived from Cellulose:** The polymers which come under this category are mainly Ethyl Cellulose, Methyl Cellulose and Hydroxy Propyl Methyl Cellulose which are extensively reported to produce a gelling effect in ocular preparations. A temperature sensitive gel formation is achieved by employing aqueous solutions of ethyl cellulose. In the previous literatures, it has been reported that when sodium dodecyl sulphate or cetyl triammonium bromide is added to ethyl cellulose in the concentration of 1%-4% weight/weight solutions, and then it is being heated around the temperatures of 30-40° centigrade, a liquid to gel transformation phase is existed which further results into the formation of very viscous and transparent gels [14].

**Poly (N-isopropylacrylamide):** This polymer is also reported as a useful polymer for providing its temperature sensitive effect in preparation of thermo reversible *In Situ* ocular gels. The phase transition from liquid to gel form is observed at a temperature of 32 ° centigrade. In the previous literature, it has been appreciated that this particular polymer has been responsible to enhance the absorption of the drug tilisolol on the ocular surface [15].

**Derivatives of Poly (Organophosphazene):** These polymers came into light in the year

1999 and were accepted as temperature sensitive polymers having biodegradable properties. These polymers have been combined with Mpeg and some esters of amino acids to give the thermo sensitive property [16]. Since then, they are used in preparation of *In Situ* gels based on temperature change. These polymers consist of both hydrophilic and hydrophobic groups and have been responsible to control the release of such drugs for a time period of 14 days for hydrophilic drugs and 21 days for hydrophobic drugs [17].

**Polymers used for pH Sensitive *In Situ* Gelling System:**

**Carbopol:** This polymer is very commonly used by the pharmaceutical industries in which *In Situ* gels based on pH sensitive mechanism is being manufactured. This polymer has an excellence of changing the sol into gel form by changing the pH. A liquid form is observed when this polymer is kept at an acidic pH but as this acidic pH is being changed into the alkaline one, this results into formation of a highly viscous and firm gel [18]. Carbopol also possess some excellent properties of mucoadhesion when distinguished from other polymers. The theory behind the activity of this polymer is that such kind of polymers have got both the acidic and basic side groups in their chemical

structure and when the pH is modified, these side groups become active in accepting or releasing protons present [19]. Carbopol provides the superiority of mucoadhesion when compared to other polymers which is based on the fact that the poly (acrylic acid)

present in this polymer forms a bond with the mucin which is further based on four different methods namely: Formation of hydrogen bonds, Interaction of hydrophobic groups, Electrostatic interaction and Inter diffusion of hydrophobic groups [20].

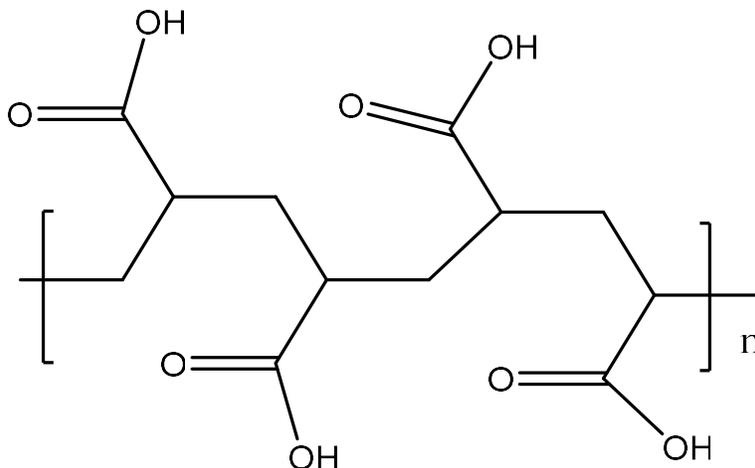


Figure 2: Depiction of Chemical Structure of Carbopol polymer

**Chitosan:** This polymer has gained much attention in the formulation of hydrogels as an important excipient. When the different polymers are being cross linked, these results into the formation of hydrogels and the physical and chemical properties of these hydrogels are very much appropriate for the delivery of drugs through the ocular surface [21]. It is reported from the previous literature that this polymer is not a single entity or molecule by its nature but it is a combination of various polymers which is made from chitin via its deacetylation process. Chitin is refereed as one of the best polymers used and it is being obtained from

crustaceans and cephalopods which form an important category of the marinal species. The formation of chitosan from its parent molecule chitin could be done in the presence of enzymes or chemicals which cause the process of deacetylation [22]. In ophthalmic formulations, chitosan has gained much acceptability due to its various attributes like adhesive property with the mucous, advantage of being biodegradable and biocompatible, superior permeability characteristics and having some fine properties of combating microbes and fungi that may render harm to the human eye. Further it does not hamper the tear film in the

eye due to its properties of pseudoplasticity and viscoelasticity [23, 24]. A good quality of chitosan which needs to be appreciated

here is that this polymer does not need the use of any additive to form a viscous gel [25].

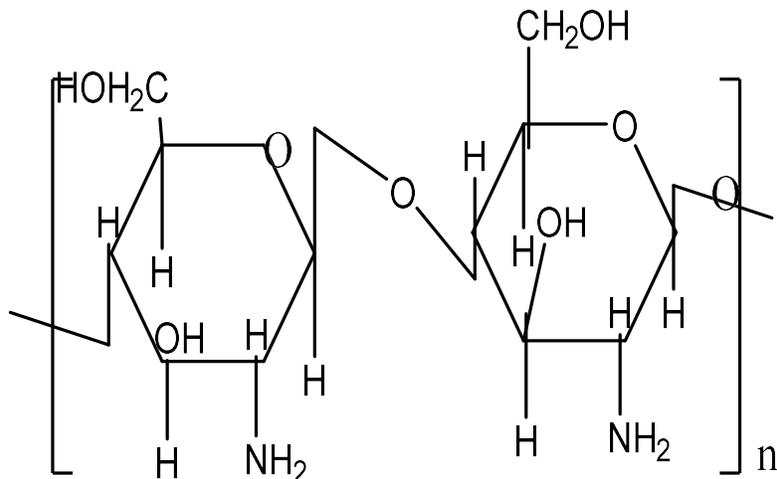


Figure 3: Depiction of Chemical Structure of Chitosan polymer

**Cellulose Acetate Phthalate Latex:** This is also referred to as Pseudolatex and is used in the preparation of pH sensitive *In Situ* gels. By the use of a previous polymer, these latexes are prepared in an artificial manner by the dispersion of this previous polymer by employing an aqueous phase. The hydrophobic drugs can also be incorporated into this latex as it is quite stable in terms of physical stability. This type of pseudolatex is also widely acceptable in the pharmaceutical industries because it provides an ease of using no organic solvent during its production. This could also be referred to as a Pseudolatex *In Situ* gelling system. The mechanism behind its acceptability in such type of Ph sensitive gelling systems is that

the sol to gel transformation takes place at a pH of 7.2 but it remains as a free flowing liquid at a pH of 4.2. Further it could be focused here that at a less pH of 5 also, it remains very much stable [26].

**Polymers based on Polyacrylic Acid:** This class of polymers came into existence when some researchers in the past prepared pH sensitive *In Situ* gels by employing Polyacrylic acid but they encountered a problem when used PAA alone as the pH of this Polyacrylic acid solution is low and it could result into a harm to the ocular surface of eye before the process of neutralizing from the fluid of tear. To overcome this problem, another polymer, HPMC was combined with Polyacrylic acid. HPMC has an attribute of

enhancing the viscosity which resulted into the creation of pH sensitive gelling systems that remain as a clear and transparent liquid at a pH of 4 but converts rapidly into a gel form at a pH of 7.4 [27].

### Polymers used for Ion Sensitive *In Situ* Gelling System:

**Sodium Alginate:** It is considered as an important vehicle in the formulation of ocular preparations because it has got suitable characteristics and properties like

biodegradability and further it has no toxicity. This polymer is commonly referred to as alginate and the mechanism which renders it as a suitable polymer for ophthalmic preparations is that it rapidly converts into a viscous gel when it comes in the vicinity of Calcium ( $\text{Ca}^{+2}$ ) and Magnesium ( $\text{Mg}^{+2}$ ) ions which results into the formation of a cross linkage by the carboxylate groups and the resulting gel formation is quite stiff and the tear fluid cannot cause any harm to it [28].

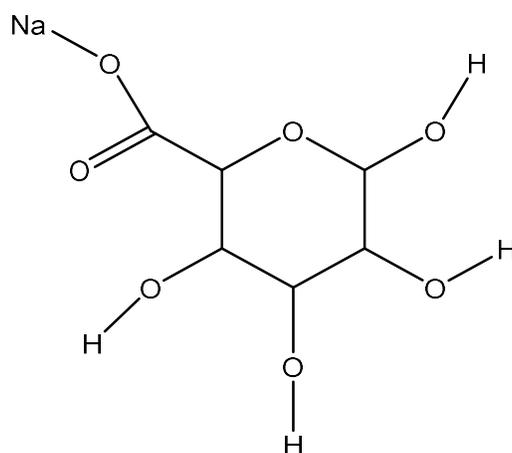


Figure 4: Depiction of Chemical Structure of Sodium Alginate

**Gellan Gum:** This also forms an important class of polymer which is used in the formulation of Ion sensitive *In Situ* gels for ocular drug delivery. It is generally obtained from a microorganism which is named as *Sphingomonas elodea*. Focusing on its structure, it contains the molecules of glucose, rhamnose as well as glucuronic acid which is present in combined forms which

results into the formation of a tetrasaccharide unit [29]. This polymer is also commonly referred to as Gelrite or Kelcogel. The mechanism behind its gel formation is that, in the presence of some monovalent and divalent cations, like Sodium ( $\text{Na}^+$ ), Potassium ( $\text{K}^+$ ), Calcium ( $\text{Ca}^{+2}$ ) and Magnesium ( $\text{Mg}^{+2}$ ) ions, this polymer gets cross linked with them and results into a

formation of very viscous and stiff gels which are suitable for administration to the surface of human eye. Such type of polymer is associated with the junction zones, having the shape of a double helix and later on, these double helical zones are transformed into 3D networks due to the presence of cations. It could also be appreciated here, that this type of gelling system could be related with the formation of hydrogen bonds, when coming in contact with the molecules of water [30].

**Carrageenan:** This polymer comes under the category of natural polysaccharide and is

helpful in the formulation of Ion sensitive gelling systems. This polymer can be viewed as coils situated in a random manner at a temperature which is higher than the temperature at which the gel is melted. When this system is cooled, it results into the formation of a 3D polymeric network in which the double helices exist as the joining units of these chains of polymers.

This polymer is further classified into three types which is depicted in the following table:

Table 2: Types of *In-Situ* Gelling Systems & Mechanisms involved [31]

Type of Carrageenan	Presence of Ions to form Gels	Properties	Applications
Iota	Potassium & Calcium ions	Elastic gel which is completely soluble in hot water	Ion Sensitive <i>In Situ</i> gelling system for Ocular Drug Delivery
Kappa	Potassium ions	Brittle gel is produced which is completely soluble in hot water	Ion Sensitive <i>In Situ</i> gelling system for Ocular Drug Delivery
Lambda	Does not induce gel formation but results into highly viscous solutions (No Ions present)	Viscous solutions which is completely soluble in cold water	High viscous polymeric solution for Ocular Drug Delivery

**Pectin:** It forms an important class of polymer which is biodegradable in nature and is an acidic carbohydrate. This polymer is obtained from plants in its natural form and present abundantly in the cell wall of plants. Looking into the structure of cell wall of a plant, it could be seen that it generally comprises of three prime layers which are primary, secondary and the middle lamella. Pectin is found plentifully in the middle

lamella. The mechanism of gelation of pectin involves the presence of Calcium ( $\text{Ca}^{+2}$ ) ions and in order to produce significant gelation, Calcium ions must be present [32]. It results into the transformation of liquid form into gel form due to the ionic environment. One of the finest properties that make this polymer superior to other polymers is that it possesses a high solubility in water and that why it does

not need to incorporate any organic solvents during the preparation of formulations.

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