IN SITU GELLING SYSTEM - AN OVERVIEW

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Summary

Over the past few decades, advances in *in situ* gel technologies have spurred development in many medical and biomedical applications including controlled drug delivery. Many novel *in situ* gel-based delivery matrices have been designed and fabricated to fulfill the ever-increasing needs of the pharmaceutical and medical fields. *In situ* gelling systems are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. *In situ* gel forming drug delivery is a type of mucoadhesive drug delivery system. The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation from which the drug gets released in a sustained and controlled manner. Many natural, biodegradable, biocompatible and synthetic polymers like alginic acid, pluronic F127, xyloglucan, gellan gum, carbopol, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone etc. are used in the preparation of *in situ* gelling system. Mainly *in situ* gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. *In situ* gelling system becomes very popular nowadays because of their several advantages over conventional drug delivery systems like sustained and prolonged release of drug, reduced frequency of administration, improved patient compliance and comfort.

Key words: *In situ* gel, biodegradable polymers, sustained and prolonged drug release.

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Introduction

For the past many years, there has been enhanced demand for more patient compliance dosage forms. As a result, the demand for their technologies has been increasing three fold annually. Since the developmental cost of a new chemical entity is very high, the pharmaceutical companies are focussing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects.

The development of *in situ* gel systems has received considerable attention over the past few years. *In situ* gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH dependent and cation induced gelation. Compared to conventional controlled release formulations, *in situ* forming drug delivery systems possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance and comfort.[1,2,3]**.** *In situ* gel forming drug delivery is a type of mucoadhesive drug delivery system. In contrast to very strong gels, they can be easily applied in liquid form to the site of drug absorption. At the site of drug absorption they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymers can be used for the production of *in situ* gels. *In situ* gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and ionic cross- linking[4,5,6]. So, i*n situ* gels are administered by oral[7], ocular[8], rectal[9], vaginal[10], injectable[11] and intra-peritoneal routes[12]. Recent advances in *in situ* gels have made it possible to exploit the changes in physiological uniqueness in different regions of the GI tract for the improved drug absorption as well as patient's convenience and compliance.

In the current niche of drug delivery technologies, *in situ* gels have made an irreplacable space because of their unique characteristics. This review presents a brief introduction to *in situ* gels, various approaches for *in situ* gelling system, different types of polymers used and evaluation of *in situ* gelling system.

Approaches for *in situ* gelling system:

The various approaches for *in situ* gelling system are:

1. **Stimuli-responsive *in situ* gel system**
   - Temperature induced *in situ* gel systems
   - pH induced *in situ* gel systems
2. **Osmotically induced *in situ* gel systems (Ion activated systems)**
3. **Chemically induced *in situ* gel systems**
   - Ionic cross linking
   - Enzymatic cross linking
   - Photo-polymerization

1. Stimuli-responsive *in situ* gel system:

Stimuli-responsive polymers are defined as polymers that undergo relatively large and abrupt, physical or chemical changes in response to small external changes in the environmental conditions. Names coined for 'stimuli-responsive' polymers have been given as stimuli-sensitive[13], intelligent[14], smart[15,16], or environmentally sensitive polymers[17]. These polymer systems might recognize a stimulus as a signal, judge the magnitude of this signal, and then change their chain conformation in direct response[18].

Temperature induced *in situ* gel systems:

Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both *in vitro* and *in vivo.* In this system, gelling of the solution is triggered by change in temperature, thus sustaining the drug release. These hydrogels are liquid at room temperature (20–25 °C) and undergo gelation when in contact with body fluids (35– 37 °C), due to an increase in temperature[19]. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach in-situ formation. The polymers which show temperature induced gelation are poloxamers or pluronics, cellulose derivatives (methyl cellulose, HPMC, ethyl (hydroxyl ethyl) cellulose (EHEC) and xyloglucan etc.

pH induced *in situ* gel systems:

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH-responsive materials. Gelling of the solution is triggered by a change in pH. At pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel[20]. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups[21]. The polymers which shows pH induced gelation are cellulose acetate phthalate (CAP) latex, carbomer and its derivatives[22] polyvinylacetal diethylaminoacetate (AEA)[23], polymethacrilic acid (PMMA), polyethylene glycol (PEG)[24], pseudolatexes etc.

2. Osmotically induced *in situ* gel systems (Ion activated systems):

In this method, gelling of the solution instilled is triggered by change in the ionic strength[25]. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na^+, Ca^{2+} and Mg^{2+} cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in the conjunctival cul-de-sac[26]. The polymer which shows osmotically induced gelation are gelrite or gellan gum, hyaluronic acid and alginates etc.

3. Chemically induced *in situ* gel systems:

The chemical reaction which forms in situ gel systems are Ionic crosslinking, Enzymatic crosslinking and Photo-polymerization.

Ionic crosslinking:-

Certain ion sensitive polysaccharides such as carragenan, Gellan gum (Gelrite), Pectin, Sodium Alginate undergo phase transition in presence of various ions such as K^+ , Ca^{2+}, Mg^{2+}, Na^+**.** These polysaccharides fall into the class of ion-sensitive ones[27]**.** For example, Alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca^{2+} due to the interaction with guluronic acid block in alginate chains.[28]

Enzymatic crosslinking:

In situ formation catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation**.**[29]

Photo-polymerization:

In situ photo-polymerization has been used in biomedical applications for over more than a decade. A solution of monomers or reactive macromer and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel[30]. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromers because they rapidly undergo photo-polymerisation in the presence of suitable photo initiator. Photopolymerizable systems when introduced to the desired site via injection get photocured *in situ* with the help of fiber optic cables and then release the drug for prolonged period of time. A photo-polymerizable, biodegradable hydrogel as a tissue contacting material and controlled release carrier is reported by Sawhney et al[31].

Polymers used as *in situ* gelling agents:-

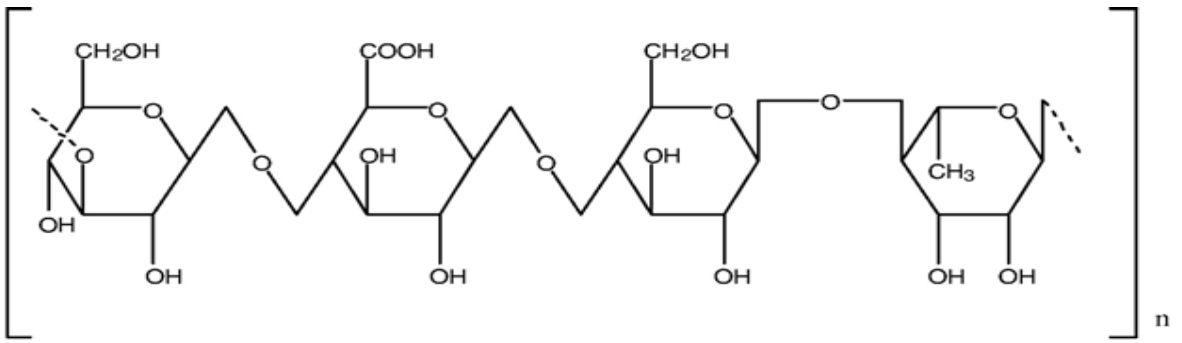
Materials that exhibit sol to gel transition in aqueous solution at temperatures between ambient and body temperature is of interest in the development of sustained release vehicles with *in situ* gelation properties.[32]

Some of the polymers used as *in situ* gelling agents are:

- Gellan gum
- Alginic acid
- Pluronic F127
- Xyloglucan
- Pectin
- Xanthum gum
- Chitosan
- Carbomer

1. Gellan gum:-

Gellan gum (Gelrite®) is a linear, anionic heteropolysaccharide secreted by the microbe *Sphingomonas elodea* (formerly known as *Pseudomonas elodea*). The polysaccharide can be produced by aerobic fermentation and then isolated from the fermentation broth by alcohol precipitation. The polymer backbone consists of glucose, glucuronic acid, and rhamnose in the molar ratio 2:1:1[33]. These are linked together to give a tetrasaccharide repeat unit . The native polysaccharide is partially esterified with L-glycerate and acetate[34], but the commercial product Gelrite has been completely de-esterified by alkali treatment[35]. Gelrite® (deacetylated gellan gum) is one of the most interesting *in situ* gelling polymers that has been tested since it seems to perform very well in humans. Gelrite® has been granted regulatory approval as pharmaceutical excipient and is marketed by Merck in a controlled-release glaucoma formulation called Blocarden® Depot (Timoptic®). Formulations with the Gelrite can be administered to ocular mucosa as a low viscosity solution. On contact with cations in tear fluid the formulation will form a clear gel[36]. This is caused by cross linking of the negatively charged polysaccharide helices by monovalent and divalent cations (Na^+, K^+, Ca^{2+}). Gellan gum produces temperature dependent or cations induced *in situ* gelling[37].



[→3)-β-D-Glcp-(1→4)- β- D -GlcpA-(1→4)- β- D - Glcp- (1→4)- α- L-Rhap-(1→]n

Fig.1. The structure of deacetylated gellan gum.

Alginic acid:

Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues joined by 1,4-glycosidic linkage[38]. Alginate is a well known polysaccharide widely used due to its gelling properties in aqueous solutions related to the interactions between the carboxylic acid moieties and bivalent counter ions, such as calcium, lead, and copper; it is also possible to obtain an alginic acid gel by lowering the environmental pH value. Dilute aqueous solutions of alginates form firm gels on addition of di and trivalent metal ions by a cooperative process involving consecutive guluronic residues in the α-L-guluronic acid blocks of the alginate chain[39]. Alginate with a high guluronic acid content will improve the gelling properties and reduce the total polymer to be introduced into the eyes. Alginate has also been proposed in the field of pharmaceutics for its *in situ* gelation properties, particularly for the application of alginate gels for ocular drug delivery, since this dosage form is so effective as compared to solutions. The systems are based on the *in situ* gelling properties of high guluronic content alginates, with experiments being carried out both in vitro, with simulated

lachrymal fluid, and *in vivo* on rabbit eyes. A prolonged delivery of two different drugs (pilocarpine[40] and carteolol)[41] was obtained in comparison to the same drugs instilled as solutions. Alginic acid is mucoadhesive[42], biodegradable and non toxic polymer. Because of these applications it is widely used as a vehicle for ophthalmic *in situ* gelling system.

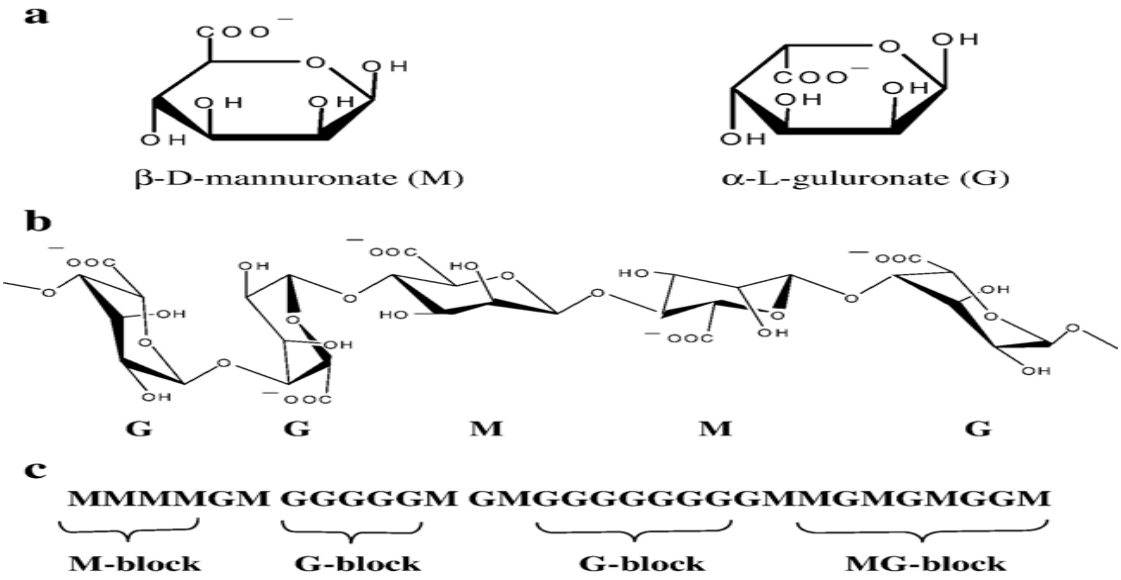


Fig.2. Structural characteristics of alginates: (a) alginate monomers (b) chain conformation and (c) block distribution.

Pluronic F127:

The Poloxamers or pluronic consist of more than 30 different non-ionic surface active agents. These polymers are ABA-type triblock copolymers composed of polyethylene oxide (PEO) (A) and polypropylene oxide (PPO) units (B). The Poloxamer series covers a range of liquids, pastes, and solids, with molecular weights and ethylene oxide–propylene oxide weight ratios varying from 1100 to 14,000 and 1:9 to 8:2, respectively[43]. Poloxamers, commercially available as Pluronic®, are the most commonly used thermal setting polymers in ophthalmology. They are formed by central hydrophobic part (polyoxypropylene) surrounded by hydrophilic part (ethylene oxide). Depending on the ratio and the distribution along the chain of the hydrophobic and hydrophilic subunits, several molecular weights are available, leading to different gelation properties. Pluronic F-127, which gives colorless and transparent gels, is the most commonly used polymer in pharmaceutical technology[44]. Poloxamer formulation generally increased drug residence time at application sites, resulting in improved bioavailability and efficacy[45]. (Pluronic® F127) was found to gel at a concentration of 20 wt. % at 25 °C, which is less than that of the other members of the Poloxamer series. At room temperature (25°C), the solution behaves as a mobile viscous liquid, which is transformed into a semisolid transparent gel at body temperature (37°C). Pluronics or Poloxamers also undergo in situ gelation by temperature change. Pluronic F-127 was used as an *in situ* gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxyl propyl methylcellulose to ensure long residence time at the application site.

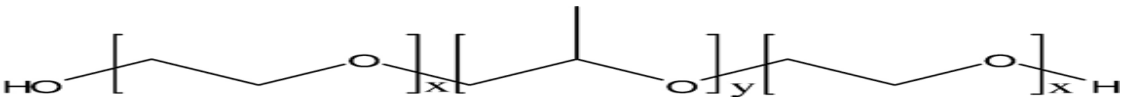


Fig.3. PEO-PPO-PEO (Poloxamer)

Xyloglucan:

Xyloglucan is a polysaccharide derived from tamarind seeds and it is composed of a (1→4)-β-D-glucan backbone which has (1→6)-α-D-xylose branches that are partially substituted by (1→2)-β-D-galactoxylose[46]. Xyloglucan forms thermo responsive gels in water, under certain conditions. When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally reversible gelation in dilute aqueous solutions. Such behavior does not occur with native xyloglucan. Gelation is only possible when the galactose removal ratio exceeds 35%[47]. The transition temperature is inversely related to polymer concentration[48] and the galactose removal ratio. For example, the sol–gel transition of xyloglucan was shown to decrease from 40 °C to 5 °C when the galactose removal ratio increased from 35 to 58%. Xyloglucan formulations were assessed for ocular delivery of pilocarpine; using Poloxamer 407 as a positive thermosensitive control. The 1.5 wt. % xyloglucan formulation enhanced the miotic response to a degree similar to that of a 25 wt. % Poloxamer 407 gel[49]. In comparison with gellan and alginate, in the oral administration of cimetidine, xyloglucan gels appear to be the system with the widest application because its gelation does not require the presence of cations, as in the case of alginate, and its use is not restricted by the charged nature of the drug, as in the case of gellan[50]. Xyloglucan gels have also been investigated for ocular delivery of pilocarpine and timolol[51,52]. The *in situ* gelling formulations were consistently more effective than aqueous buffer solutions while the rapid gelation was essential in preventing the loss of drug by drainage from the eye. Xyloglucan gels have also been used as vehicles for a sustained release of percutaneous formulations of non-steroidal anti-inflammatory drugs[53].

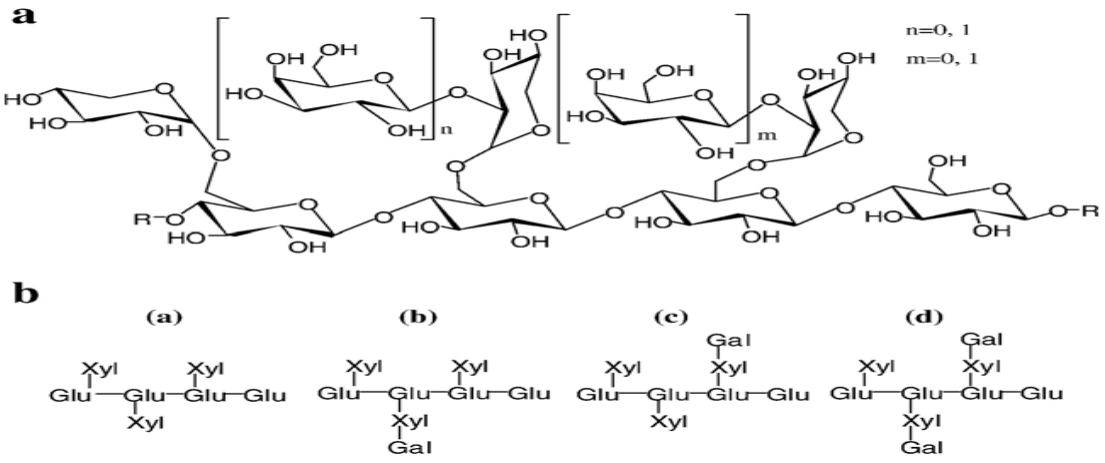


Fig.4. a: The structure of the repeating units of xyloglucan. b: The unit structures of oligosaccharides from tamarind xyloglucan showing (a) heptasaccharide, (b) and (c) octasaccharide, and (d) nonasaccharides

Pectin:

Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α- (1-4)-D-galacturonic acid residues. Low methoxypectins (degree of esterification <50%) readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains in a manner described by egg-box model . Although the gelation of pectin will occur in the presence of H + ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery[54]. The main advantage of using pectin for these formulations is that it is water soluble, so organic solvents are not necessary in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is administered orally. Calcium ions in the complexed form may be included in the formulation for the induction of pectin gelation[55]. Sodium citrate may be added to the pectin solution to form a complex with most of calcium ions added in the formulation. By this means, the formulation may be maintained in a fluid state (sol), until the breakdown of the complex in the acidic environment of the stomach, where release of calcium ions causes gelation to occur. The quantities of calcium and citrate ions may be optimized to maintain the fluidity of the formulation before administration and resulting in gelation, when the formulation is administered in stomach. The potential of an orally administered in situ gelling pectin formulation for the sustained delivery of Paracetamol has been reported[56].

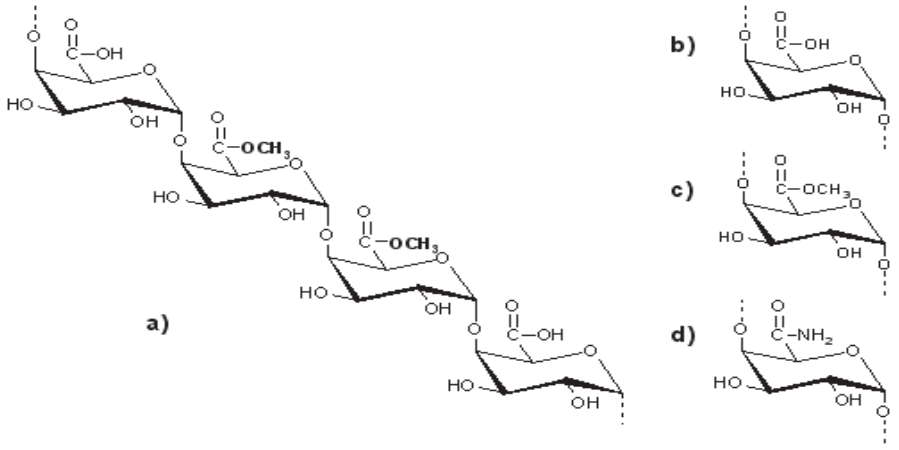


Fig. 5 (a) A repeating segment of pectin molecule and functional groups: (b) carboxyl; (c) ester; (d) amide in pectin chain.

Xanthum gum:

This polymer was discovered in the 50's in the course of a screening to identify micro organisms that produced water soluble gums of commercial interest. The first industrial production was carried out in 1960 and the polysaccharide became commercially available in 1964. Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris.* Since its discovery xanthan has been widely studied and used as tablet excipient to increase the drug rate of delivery. Xanthan (Fig.5) has a cellulosic backbone of D-glucose linked β-1, 4. For every alternate glucose there is a side chain consisting of β-D-mannose-(1,4)-β-D-glucuronic acid- (1,2)-α-D-mannose. The terminal mannose moiety may carry pyruvate residues linked to the 4-and 6-positions. The internal mannose unit is acetylated at C-6. The degree of substitution for pyruvate usually varies between 30 and 40% whereas it is as high as 60–70% for acetate. Xanthan has also been tested for the preparation of sponge like *in situ* gelling inserts for the delivery of proteins and peptides in the nasal cavity[57]. With xanthan and other like polymers such as carrageenan, the drug release was the result of a complex interplay of osmotic forces, water uptake and electrostatic interactions between drug and polymer. Since the major problem with nasal delivery is the mucociliary clearance, bioadhesive polymers can be used to increase the nasal residence time. This ensures the formation of highly porous polymeric sponges into which the drug is embedded. Xanthan is more efficient than alginate and carrageenan in recovering the sponge-like structure after a compression, i.e. showed a better elasticity in comparison to the other tested polymers.

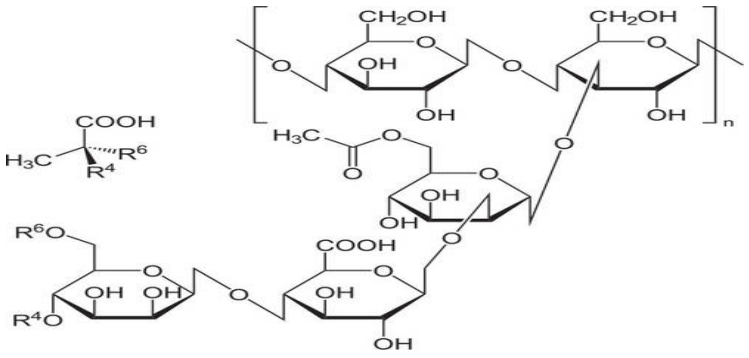


Fig. 6. Repeating units of xanthum gum

Chitosan:

Chitosan is obtained from chitin by deacetylation reaction usually carried out in alkaline medium, a natural component of shrimp and crab shell. Chitosan exhibits several favorable properties such as biodegradability and biocompatibility[58]. It also has mucoadhesive properties due to its positive charge at neutral pH that enable an ionic interaction with the negative charges of sialic acid residues of mucus[59,60]. It is a biocompatible, pH-dependent cationic polymer, which is soluble in water up to pH 6.2. Basification of chitosan aqueous solutions above this pH leads to the formation of an hydrated gel-like precipitate. Chenite et al.[61,62] developed a novel approach to produce thermally sensitive neutral solutions based on Chitosan / polyol salt combinations. Thus the terms chitin and chitosan describe a continuum of copolymers of N- acetyl-D-glucosamine

and D-glucosamine residues, the two being distinguished by insolubility or solubility in dilute aqueous acid solutions. Chitosan-based gels may be broadly divided into thermally non-reversible gels and the far smaller group of thermally reversible gels. Within the first group a further subdivision into those formed by N-acylation and those produced by Schiff's base (aldimide) formation is useful, and this division of the topic is used here.

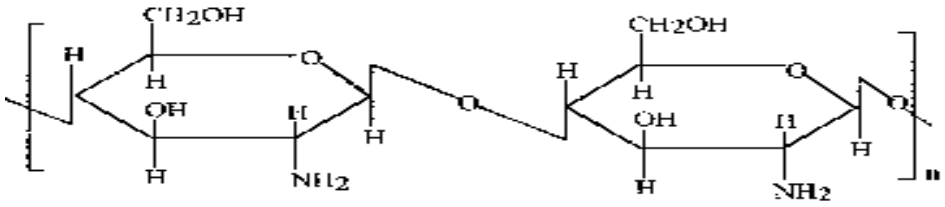


Fig. 6. The structure of chitosan

Carbomer:

Cross-linked poly (acrylic acid) (Fig.7) of high molecular weight, commercially available as Carbopol®, is widely used in ophthalmology to enhance precorneal retention to the eye[63]. Carbopol® 934 is a synthetic polymer composed of 62% of carboxyl groups with a high molecular weight (approximately 3×106) formed by repeating units of acrylic acid, cross-linked with either allylsucrose or allylethers of pentaerythritol[64]. Carbopol offers the advantage of exhibiting excellent mucoadhesive properties when compared with other polymers (e.g. cellulose derivatives, and polyvinyl alcohol). As the concentration of Carbopol increases in the vehicle, its acidic nature may cause stimulation to the eye tissues. In order to reduce the total polymer content and improve the gelling properties, an ocular drug delivery system based on a combination of Carbopol and methylcellulose has been developed[65]. Carbopol is a polyacrylic acid (PAA) polymer, which shows a sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5[66]. A pH induced *in situ* precipitating polymeric system (an aqueous solution of carbopol-HPMC system) was designed and developed by Ismail et al. for plasmid DNA delivery[67].

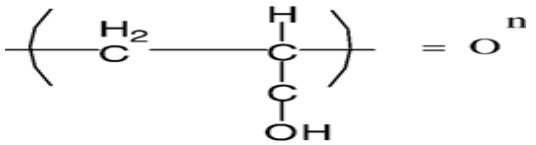


Fig.7. The structure of carbomer.

Synthetic polymers:

Synthetic polymers are of increasing interest in drug delivery as therapeutic agent. Synthetic polymers are popular choice mainly for parenteral preparations. Aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide- coglycolide), poly (decalactone), poly ε-caprolactone have been the subject of the most extensive recent investigations[68].Various other polymers like triblock polymer systems composed of poly (D,L-lactide)-block poly

(ethylene glycol)-block-poly (DL-lactide), blends of low molecular weight poly (D,L-lactide) and poly (ε-caprolactone) are also in use. These polymers are mainly used for the injectable *in situ* formulations. The feasibility of lactide/glycolide polymers as excipients for the controlled release of bioactive agents is well proven.

Evaluation of in situ gelling system:

The prepared in situ gel formulations were evaluated for clarity, pH measurement, gelling capacity, drug content, rheological study, Fourier transform infra-red spectroscopy and Thermal analysis, in vitro diffusion study, antibacterial activity, and accelerated stability studies.

Clarity:

The clarity of formulated solutions can be determined by visual inspection under black and white background.

Viscosity:

The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route of administrations) were determined with different viscometer like Brookfield viscometer, Cone and Plate viscometer. The viscosity of these formulations should be such that it should be patient compliant[69].

Texture analysis:

The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringability of sol so the formulation can be easily administered *in vivo*. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surfaces like tissues[70]**.**

Sol-Gel transition temperature and gelling time:

For *in situ* gel forming systems, the sol-gel transition temperature and pH should be determined. Gelling time is the time required for first detection of gelation of *in situ* gelling system[71]. Thermo sensitive *in situ* gel should be checked for *in situ* gelling at body temperature.

Gel-Strength:

This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker, from the sol form. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface[72]**.**

Drug-polymer interaction study and thermal analysis:

Interaction study can be performed with Fourier Transform Infra Red (FTIR) spectroscopy. During gelation process, the nature of the interacting forces can be evaluated using the technique by employing KBr pellet method. Thermo gravimetric Analysis (TGA) can be conducted for *in situ* forming polymeric system to quantitate the percentage of water in hydrogel. Differential Scanning calorimetry (DSC) conducted to observe if there are any changes in thermograms as compared with pure active ingredients used for gelation[73].

***In vitro* drug release studies:**

For the *in situ* gel formulations to be administered by oral, ocular or rectal routes, the drug release studies are carried out by using the plastic dialysis cell[74] . The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The sol form of the formulation is placed in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analyzed for the drug release using analytical technique[75]. For injectable *in situ* gels, the formulation is placed into vials containing receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed[76]**.**

Antibacterial activity:

The microbiological growth of bacteria is measured by concentration of antibiotics and this has to be compared with that produced by known concentration of standard preparation of antibiotic. To carryout microbiological assay serial dilution method is employed[77].

Accelerated stability studies:

Formulations are placed in ambient colour vials and sealed with aluminium foil for a short term accelerated stability study at 40±2 °C and 75±5% RH as per International Conference on Harmonization (ICH) Guidelines. Samples are analyzed every month for clarity, pH, gelling capacity, drug content, rheological evaluation, and *in vitro* dissolution.[78]

Marketed products of *in situ* polymeric system:

Timoptic-XE:

Timolol maleate ophthalmic gel forming solution is a non-selective beta-adrenergic receptor blocking agent. It is registered trademark of MERCK & CO., Inc. Timoptic-XE sterile ophthalmic gel forming solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths. The pH of the solution is approximately 7.0, and the osmolarity is 260-330 mOsm. Each mL of Timoptic-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of Timoptic-XE 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate).

AzaSite:

AzaSite is a marketed product of InSite Vision which has been approved in april 2007. AzaSite is a topical ophthalmic solution of azithromycin formulated in DuraSite (polycarbophil, edetate disodium, sodium chloride). AzaSite is supplied as a sterile aqueous ophthalmic formulation designed for topical administration. The recommended initial dose of the drug is instill 1 drop in the affected eye(s) twice daily, eight to twelve hours apart for the first two days and then instill 1 drop in the affected eye (s) once daily for the next five days.

Pilopine HS:

Pilopine HS is a marketed product of Alcon Laboratories Inc. Pilopine HS (pilocarpine hydrochloride ophthalmic gel) 4% is a sterile topical ophthalmic aqueous gel which contains more than 90% water and employs Carbopol-940, a synthetic high molecular weight cross-linked polymer of acrylic acid, to impart a high viscosity.

Akten™ :

Akten™ is an HPMC-based gel of lidocaine hydrochloride for ocular surface anesthesia. Akten™ contains 35 mg of lidocaine hydrochloride per mL as the active ingredient. Akten™ also contains Hypromellose, Sodium Chloride, and Purified Water as inactive ingredients. The pH may be adjusted to 5.5 to 7.5 with Hydrochloric Acid and/or Sodium Hydroxide. The recommended dose of Akten™ is 2 drops applied to the ocular surface in the area of the planned procedure. Akten™ may be reapplied to maintain anesthetic effect.

Virgan:

Vigran is an ophthalmic antiviral that is indicated for the treatment of acute herpetic keratitis. The recommended dosing regimen for Virgan is 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) unti the corneal ulcer heals, and then 1 drop 3 times per day for 7 days. Virgan (ganciclovir) contains carbomer 974. The carbomers are polyacrylic acid derivatives that impart high viscosity to their aqueous solutions at neutral pH (above their pKa values) due to ionization and hydration of the carboxyl groups.

Cytoryn:

This is one of the Macromed's products, which is a novel, peritumoral, injectable depot formulation of interleukin-2 (IL-2) for cancer immunotherapy using Regel drug delivery system. It is a free flowing liquid below room temperature that instantly forms a gel depot upon injection from which the drug is released in a controlled manner. Cytoryn enhances the immunological response by safely delivering four times the maximum tolerated dose allowed by conventional IL-2 therapy. Cytoryn also activates the systemic antitumor immunity. Regel system stabilizes and releases IL-2 in its bioactive form. The release of drugs is controlled by the rate of diffusion from and degradation of the depot.

Conclusion:

Drug delivery has undergone a revolutionary advancement in the past few years. With the advent of novel delivery systems, various drug molecules have been revived of their therapeutic and commercial benefits. The introduction of *in situ* gelling systems has further strengthened the link between therapeutic need and drug delivery. A lot of research is ongoing in various laboratories to explore *in situ* gel as drug delivery systems for better patient care. The utility of *in situ* gelling system in drug delivery and biomedical application is immense. Over the last decade, an impressive number of novel *in situ* gel-forming systems have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular system depends on its intrinsic properties and envisaged therapeutic use. Nowadays, *in situ* gelling system has become the alternative of conventional dosage form because of its controlled drug release, use of water soluble and biodegradable polymers, biocompatibility and better patient compliance by reducing dosing frequency.

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