ORAL IN-SITU GEL FOR PERIODONTITIS: A REVIEW

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ABSTRACT

In the past few years, an increasing number of in situ-forming systems have been reported in the literature for various biomedical applications including drug delivery systems. In this review, we highlight the methods of oral in-situ hydrogel in the context of drug delivery and tissue repairing for periodontitis. Oral in-situ gel is found to be the most suitable type of formulation for the treatment of periodontitis, that delivers the drug locally, as a result, dose can be reduced as well as toxicity can be minimised. There are several possible mechanisms that lead to in situ gel formation: solvent exchange, UV-irradiation, ionic cross-linkage, pH change, and temperature modulation. The article provides insight on natural polymers as well as synthetic polymers, including systems based on thermally triggered system, pH triggered system, ionic cross linking method, enzymatic cross linking method etc. Lastly, this review summarize about the characterization of oral in situ gels including different evaluation such as drug content study, pH & viscosity determination, texture analysis, spreadibility, gel strength, gelling time, sterility testing, in-vitro drug release study, stability study etc.

KEYWORDS: Periodontitis, in-situ, Oral Gel, Polymers, Evaluation.

INTRODUCTION

Gel is the state which exists between solid and liquid phase. The solid component comprises a three dimensional network of inter-linked molecules which immobilizes the liquid phase.\(^1\)

In situ gelation is a process of gel formation at the site of action after the formulation has been applied at the site. In situ gel phenomenon based upon liquid solution of drug formulation and converted into semi-solid mucoadhesive key depot.\(^2\) In situ gel forming formulations are currently a novel idea of delivering drugs to patients as a liquid dosage form,
yet achieve sustained release of drug for the desired period. Different delivery systems based on polymers have been developed, which are able to increase the residence time of the formulation at absorption site of drugs. Also its mucoadhesive property prevent it from getting washed by salivary fluid inside the buccal cavity. In recent years, there has been an increasing interest in water soluble polymers that are able to form gels after application to delivery site. These so called in situ gelling polymers are highly advantageous compared with other polymers because, 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. Hydrogels are the polymeric materials with three dimensional networks, which have gained much attention in biomedical fields as carriers for drugs, protein, cells, and others because of their good biocompatibility, solute permeability and tunable release characteristics. The retaining ability of a large amount of water within their structures which results in high water content and soft-surface properties is the character that makes them compromised on the surrounding tissues and leads to a good biocompatibility. Because of the present busy life system even in common man dental diseases are most widespread chronic disorders. Periodontal disease refers to a group of problems that arise in the sulcus, the crevice between the gum and tooth the common causative organisms includes Actinobacillus, actinomycetemcomitans as a pathogen responsible for juvenile periodontitis, staphylococci subspecies epidermidis and aureus are responsible adult periodontal disease. Site-specific therapy for periodontitis has three potential advantages, it decreased drug doses, increased drug concentration at the site of infection and reduced systemic side effects such as gastrointestinal distress. Periodontal diseases treatment with a localized drug delivery system aims at delivering therapeutic agent at sufficient level inside the periodontal pocket and at the same time minimizing the side effects associated with systemic drug administration. Thus it increases patient’s compliance.

Chitosan, the second most abundant natural polysaccharides next to cellulose, is one of the most widely used, has many advantages over other polymers, like nontoxicity, biocompatibility and biodegradability. Chitosan is a family of cationic polysaccharides with a basic chemical structure of (1, 4)-linked 2-amino-2-deoxy-D-glucans, which are produced commercially by the partial deacetylation of chitin obtained from the reprocessing of seafood waste. Members of the chitosan family differ in terms of their molecular weight and degree of
deacetylation.\textsuperscript{[7]} Chitosan is biodegradable, as it is broken down in the human system to harmless products (amino sugars) that can be easily absorbed.\textsuperscript{[11-12]}

**Periodontitis:** Periodontitis is term used to describe some pathological conditions characterized by degeneration and inflammation of gums, periodontal ligaments, alveolar bone, and dental cementum.\textsuperscript{[13]} It is a localized inflammatory reaction caused by bacterial infection of a periodontal pocket accompanying with subgingival plaque. Although bacteria are the principal cause of periodontal disease, the appearance of microbial pathogenic factors alone may not be enough to cause periodontitis. Periodontal pathogens generate destructive by-products and enzymes that break extracellular matrices as well as host cell membranes to produce nutrients for their growth. In doing so, they start damage directly or indirectly by triggering host mediated responses that lead to self injury. In the early phase of the disease, inflammation is localized to the gingiva called gingivitis but extends to deeper tissues in periodontitis, leading to gingival swelling, bleeding, and bad breath. In the late phase of the disease, the supporting collagen of the periodontium is disintegrated, alveolar bone begins to resorb, and gingival epithelium migrates along the tooth surface forming a ‘periodontal pocket system.’\textsuperscript{[14]}

Periodontitis shows many signs and symptoms such as swollen or puffy gums, bright red, dusky red or purplish gums, gums feel tender when touched, gums bleed easily, gums pull away from teeth making teeth look longer than normal, new spaces developing between teeth, pus between teeth and gums, bad breath, loose teeth, painful chewing etc.\textsuperscript{[13]}

![Fig. 1: Periodontal disease affected teeth.](image_url)

**IN-Situ Oral Gel:** The major importance is the possibilities of administrating accurate & reproducible quantities compared to already formed gel. In-situ forming polymeric delivery system such as ease of administration & reduced frequency of administration improved
patient compliance & comfort. Poor bioavailability & therapeutic response exhibited by conventional dosage form due to rapid metabolism and elimination of drug may be overcome by use of gel system that are instilled locally.\textsuperscript{[15]}

**Advantages of in-situ oral gel\textsuperscript{[16-17]}**

- Low dose is required for treatment.
- Minimum local and systemic side effects.
- Ease of application.
- Reduced frequency of drug administration.
- Improved patient compliance and comfort.
- Increased residence time.
- Improved bioavailability.
- It can also be administered to unconscious patient.

**Disadvantages of in-situ oral gel**

- It is more susceptible to stability problems due to chemical degradation.
- It requires high level of fluids.
- It leads to degradation due to storage problems.

**Limitations:** The quantity and homogeneity of drug loading into hydrogels may be limited, particularly for hydrophobic drugs. Only drugs with small dose requirement can be given. Lower mechanical strength, may result into premature dissolution or flow away of the hydrogel from a targeted local site. The high water content and large pore size of most hydrogels often result in relatively rapid drug release. Eating and drinking may become restricted up to few hours.

**Ideal characteristics of a suitable drug candidate**

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose up to 40 mg.
- The drug should have smaller and moderate molecular weight.
- The drug should have good stability and solubility in water.
- It should be partially unionized at the pH of oral cavity.
- It should have ability to permeate the oral mucosal tissue.
Ideal properties of polymers for in-situ gels

- The polymer employed should be non-toxic, nonirritant and devoid of leachable impurities.
- It should have good wetting and spreadability property.
- The polymer should exhibit sufficient peel, shear and tensile strengths.
- The polymer should be readily available and should not be very expensive.
- It should have good shelf life.
- It should not aid in cause secondary infections in the oral mucosa/dental region.
- It should have a good mouth feel property.
- It would be ideal to have a polymer that would have local enzyme inhibition action along with penetration enhancing property.

Approaches in in-situ gel drug delivery: For triggering the in-situ gel formation of biomaterials, four broadly defined mechanisms are used: Physiological stimuli (e.g., temperature and pH), physical changes in biomaterials (e.g., solvent exchange and swelling), chemical reactions (e.g., enzymatic, chemical and photo-initiated polymerization).[18]

Thermally trigged system: Temperature-sensitive hydrogels are probably the most commonly studied. 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 ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is faccilated and no external source of heat other than that of body is required for trigger gelation. Three main strategies exists in engineering of thermoresponsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels. Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST) and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature is used for this purpose. A positive temperaturesensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate) have positive temperature dependence of swelling. The most commonly used thermoreversible gels are these prepared from poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide). Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature.[19-20]
**pH triggered systems**: Another formation of in situ gel based on physiologic stimuli is formation of gel is induced by pH changes. All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. 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] Polyvinylacetal diethylaminoacetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition. Drug formulated in liquid solutions have several limitations, including limited bioavailability and propensity to be easily removed by salivary fluid.[22] Mixtures of poly(methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) also has been used as a pH sensitive system to achieve gelation.[23]

**Swelling**: In situ formation may also occur when material absorbs water from surrounding environment and expand to occupy desired space. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in-vivo by enzymatic action.[24]
Diffusion: This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.[25]

Ionic crosslinking: Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones. While k-carrageenan forms rigid, brittle gels in reply of small amount of K⁺, i-carrageenan forms elastic gels mainly in the presence of Ca²⁺. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca²⁺, Mg²⁺, K⁺ and Na⁺. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca²⁺. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca²⁺ due to the interaction with guluronic acid block in alginate chains.[26-27]

Enzymatic cross-linking: 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. 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 be injected before gel formation.[28]

Fig. 4: Enzymatic cross linking mechanism.
**Photo-polymerisation**: Photo-polymerisation is commonly used for in situ formation of biomaterials. 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. 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 photoinitiator. Typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet is not used often because it has limited penetration of tissue and biologically harmful. A ketone, such as 2,2 dimethoxy-2-phenyl acetophenone, is often used as the initiator for ultraviolet photo-polymerization, where as camphorquinone and ethyl eosin initiators are often used in visible light systems.\[29\] These systems can be designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence in vivo. Photo-polymerizable systems when introduced to the desired site via injection get photo-cured in situ with the help of fiber optic cables and then release the drug for prolonged period of time. The photo-reactions provide rapid polymerization rates at physiological temperature. Furthermore, the systems are easily placed in complex shaped volumes leading to an implant formation.\[30\]

**Types of polymers used in in-situ gelling system**

**Pectin**: Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α-(1-4)-Dgalacturonic acid residues. Low methoxypectins 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. 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.\[31-32\]

**Xyloglucan**: Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod like chains. The sol-gel transition temperature varies with the degree of galactose elimination. It forms thermally reversible gels on warming to body temperature.\[33-35\]
Gellangum: Gellan gum (commercially available as Gelrite TM or Kelcogel TM) is an anionic deacetylated exocellular polysaccharide secreted by *Pseudomonas elodea* with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It has the tendency of gelation which is temperature dependent or cations induced. This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water. The formulation consisted of gellan solution with calcium chloride and sodium citrate complex.\[35-36\]

Alginic acid: Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. The proportion of each block and the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form firm gels on addition of di- and trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-L-glucuronic acid blocks of the alginate chain.\[37\]

Xanthum gum: Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (βD-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronicacid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain.\[38\]

Chitosan: Chitosan is a biodegradable, thermosensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.236. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution.\[39-40\]
Carbopol

Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution, while reducing the acidity of the solution. Various water soluble polymers such as carbopol system- hydroxypropylmethylcellulose system, poly (methacrylic acid)-poly (ethylene glycol) come under the category of pH-induced in-situ precipitating polymeric systems.\[41\]

Evaluation of oral in-situ gelling system

Clarity: The clarity may be determined by visual inspection under the 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 and may be determined with different viscometer like Brookfield viscometer, cone and plate viscometer. The viscosity of these formulations should be such that it should be patient compliance.\[44\]

pH: Measurement of pH was done by using a digital type pH meter by dipping the electrode completely into the gel so as to cover the electrode.\[44\]

Texture analysis: The firmness, consistency and cohesiveness of formulation may be determined using texture analyzer which mainly indicates the syringe ability of sol so the formulation can easily administered in-vivo.\[42\]

Spreadability: About 1 gm of gel was weighed and kept at the center of the glass plate (10 x 10 cm) and another glass plate was placed over it carefully. 2 kg weight was placed at the center of the plate and care should be taken to avoid sliding of the plate. After 30 min the diameter of the gel in cm was measured.

Drug content: Take 1ml of formulation and adjust to 10ml in volumetric flask and then dilute with 10ml of distilled water, 1ml from this solution again diluted with distilled water up to 10ml. After this take absorbance of prepared solution at a particular wavelength of the drug by using U.V visible spectroscopy.

Gel strength: This parameter may be evaluated using a rheometer. Depending on the mechanism of the gelling agent used a specified amount of gel is prepared in beaker, from the
sol form. This gel containing beaker is raised at 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 gel surface."^{43}"

**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 the first detection of gelation of in-situ gelling system. Thermo sensitive in-situ gel should be checked for in-situ gelling at body temperature."^{43}"

**Sterility testing:** Sterility testing is carried out as per the IP 1996. Incubate the formulation for not less than 14days at 300°-350°C in the fluid thioglycolate medium to find the growth of bacteria and at 200°-250°C in soyabean casein digest medium to find the growth of fungi in formulation.

**Accelerated stability studies:** Formulation is replaced in amber colored vials and sealed with aluminum foil for the short term accelerated stability at 40°±20°C and 75±5% RH as per ICH state guidelines."^{42}"

**In vitro drug release studies:** The drug release studies are carried out by using the plastic dialysis cell. 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 receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed."^{43}"

**CONCLUSION**

In conclusion, it can be stated that in order to develop broadly applicable hydrogels we must accomplish three-dimensional patterning of polymer gradients within hydrogels, both in terms of bioactive functional groups and scaffold material properties. The gelling process should occur under mild conditions for biomedical applications without damaging incorporated pharmaceuticals and cells. Therefore, cross links have been prepared in simple chemical reactions such as ionic-polymerization. The types and forms a polymeric system affect the biocompatibility of an in situ gelling system. The cross links in the gel can be
chemically connected or physically associated forms. Depending on the type of the cross links; the degradation of the material will give different chemical entities as soluble degradation products. Also, porosity of the gel should be considered in selecting a specific application of the in situ gelling system. Finally, the chemicals used to induce gelation such as residual monomers, initiators, and cross linking agent should be carefully selected. Biocompatibility issues between the polymers and incorporated drugs are particularly important in the in situ gelling system. Introduction of very reactive functional groups to polymers facilitates the cross linking reactions of the polymer in the gel-forming procedure, but the functional groups may also show cross-reactivity with incorporated pharmaceuticals or cells after the gel formation as well as during as well as in situ gelation.

REFERENCE


