Iraqi Journal of Pharmacy 21(3) (2024) 89-101

Online ISSN: 2664-2522

Print ISSN: 1680-2594

Iraqi Journal of Pharmacy

Journal homepage : https://iphr.mosuljournals.com

Review Article:

In-situ Gelling System: A Promising Delivery Method for Treating Periodontitis

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Article Information

Article history:
Received on: 06 March 2024
Revised on: 18 April 2024
Accepted on: 01 May 2024
Published on: 01 September 2024

Keywords:
Periodontitis,
periodontal diseases,
In-situ gel,
Poloxamer,
Carbopol,
Gellan gum.

Abstract

Background: Periodontitis is a chronic and potentially severe inflammatory disease that can affect both men and women. It is caused by various factors such as inadequate oral health, stress, consumption of alcoholic beverages, cigarette smoking, food, some immunity-related diseases, and chronic diseases. If left untreated, these disorders can ultimately contribute to missing teeth and other mouth diseases. Various delivery systems like fibers, stripes, films, and microparticulate systems are available to treat periodontitis. *In-situ* drug delivery systems use stimuli-sensitive polymers that undergo a solution-to-gel phase transition, which enables them to cover the entire pocket. As a result, they are more effective in treating periodontitis than other delivery systems. **Aim:** Provide an overview of periodontitis, its therapies, and how an in-situ gelling system can treat it effectively and safely. **Methods:** To achieve this aim, an extensive systematic search was done in different databases, including Science Direct, Springer, PubMed, ResearchGate, and Google Scholar, so many of the related prior research were reviewed. **Conclusion:** *In-situ* gelling systems are encouraging drug delivery systems for treating periodontitis. because of their ability to deliver drugs at the site of infection while decreasing the possibility of side effects. These systems containing biocompatible, biodegradable, and water-soluble polymers have promising results in improving the treatment of periodontitis.

1. Introduction

Many vertebrates possess teeth in their mouth or jaw that aid in the consumption, grinding, and tearing of food. A tooth is composed of two main parts: the crown and the root (1). To maintain good oral hygiene, it is important to clean your teeth regularly to remove plaque from the tooth surface. This helps prevent tooth decay, gingivitis, and infections around the teeth (2).

The cervical line is a distinct indentation that separates the tooth's root and crown, marked by a visible boundary where the tooth emerges from the gum line and the crown's enamel meets the root's cementum. Dentists rely on this essential feature to diagnose and treat various dental conditions, such as gum disease and tooth decay. It is crucial to understand the anatomy of teeth and the location of the cervical line for maintaining good oral health (3). The tooth's enamel, a complex and transparent surface, protrudes from the jaw bone in the form of a crown. The root of the tooth, an anchor made of alveolar bone, provides blood and nerves through the apical foramen (4).

Periodontal diseases refer to many chronic inflammatory diseases affecting the gums, bone, and ligaments supporting the teeth. These conditions can cause damage to the soft tissues surrounding the teeth and the connective tissue collagen fibers that anchor a tooth to the alveolar (5). At the beginning of Periodontal disease, inflammation of the gum tissue (gingivitis) is caused by bacteria in plaque, a biofilm that builds up on teeth and gums.

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How to cite:

Abdulla, A., R., Alfahad, M., A., Alfahad, Hameed, Z., A., (2024). In-situ Gelling System: A Promising Delivery Method for Treating Periodontitis. Iraqi J. Pharm. 21(3), 89-101.

DOI: **https://doi.org/10.33899/iraqij.p.2024.147513.1090**

Periodontitis is a prevalent disorder with a global prevalence of 11% for the severe form of the disease (6). Periodontal disease is an infection caused by gram-negative bacteria that affects the periodontal pocket. Symptoms include plaque that accumulates below the gum line (9), inflammation, and degeneration of the alveolar bones (10). It has been identified that human dental plaque contains up to 800 different microbial species like Porphyromonas gingivalis, Bacteroides forsythus, Aggregatibacter actinomycetemcomitans and Fusobacterium nucleatum, etc. Research suggests that microbial membranes may play a role in the development of periodontitis (7). By learning more about the underlying causes of this disease, we can work towards developing more effective treatments and prevention strategies (8).

One of the common periodontal diseases is called the Plaque induced gingivitis which is caused by bacterial growth in dental plaque, an adhesive membrane that forms on the tooth and gum. When left untreated, gingivitis can progress to periodontitis, which can cause severe damage to the teeth and gums, leading to tooth loss and other+ health complications. Maintaining good oral hygiene practices is essential to prevent the onset of gingivitis and other oral health problems (9). **Figure 1** shows the stages of periodontal diseases (10). In the early stage, gingivitis is characterized by symptoms like gingival swelling, bleeding, and bad breath (11). In the chronic phase of periodontitis, there is degeneration of the supporting collagen, periodontal ligament, and alveolar bone, which results in the formation of a pocket in the gums (12). The pH range within the pocket surrounding the teeth may fluctuate between 6 and 7 (13). Periodontitis can cause gums pockets with probing depth ranging from 4-8mm (Millimeters) or more. Treatment is needed for pockets with a probing depth of 5mm or more (8). Bacteria and some calculus are usually present in a healthy gingival pocket and are controlled by the immune system (14). The pus formation is caused by an immediate inflammatory reaction when the pocket gets deeper, disturbing the equilibrium. The debris and swelling disrupt the usual fluid movement in and out of the pocket, accelerating the inflammatory cycle (3). More oversized pockets are more likely to collect food particles and create new sources of infection (15).

Periodontitis, If left untreated, periodontitis can result in tooth loss and a decline in the quality of life (16). Patients often experience reduced self-esteem and poor esthetics, which negatively affect their daily life (17). In addition, periodontitis can worsen the advancement of certain diseases, such as diabetes mellitus (18), atherosclerosis, chronic obstructive pulmonary disease (20), and to the onset and advancement of Alzheimer's disease (21).

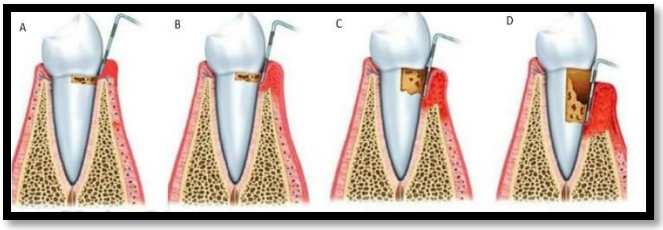

Figure 1. The stages of periodontal disease. panel A early signs of gingivitis. Panel B mild periodontitis (probing depth ≤ 4 mm, CAL ≤ 1-2 mm), Panel C moderate periodontitis(probing depth ≤ 5 mm, CAL ≤ 3-4 mm), Panel D severe periodontitis(probing depth ≥ 6 mm, CAL ≥ 5 mm). (CAL: Clinical attachment loss) The figure was adapted from reference (10).

In-situ gelling systems are polymeric formulations that undergo a phase transition from solution to gel when applied to the human body (22). This transformation is caused by a specific trigger, such as body temperature, as in the case of thermosensitive in-situ gel (23). In the production of in-situ gel formulations, a variety of polymers are utilized, such as thermosensitive (34), ion-responsive (35), and pH-responsive polymers (24). Polymers are highly versatile and can deliver various molecules with varying release rates (25). As per the information provided, in-situ gels are a type of drug delivery system that are administered orally (26), ocularly (27), rectally (28), vaginally (29), through injection (30), and intraperitoneal (31).

In-situ gelling systems offer several advantages due to their ability to administer medication conveniently. These systems increase local bioavailability, allowing the medication to effectively reach its intended target. Additionally, they help reduce the dosage concentration, leading to less frequent dosing. This not only improves patient convenience but also enhances their compliance and comfort during treatment. In-situ gelling systems can significantly improve treatment outcomes and enhance the patient experience (32). The formulation has been simplified, lowering investment and manufacturing costs (33). This review aims to provide an overview of the danger of periodontitis, its current therapies, and how an in-situ gelling system can deliver safe and effective local treatment for periodontitis.

2. Methods

A comprehensive exploration was carried out on the databases of Science Direct, Springer, PubMed, ResearchGate, Google Scholar, and additional sources between September 2023 and March 2024. The terms "periodontitis, periodontal diseases, in-situ gel, poloxamer, carbopol, chitosan, gellan gum" were utilized either separately or in combination. To find the articles that the aforementioned electronic search engines were unable to locate, we manually searched the reference lists of the

included research. The primary prerequisite for research inclusion in this review is publication within the timeframe of 2000 to 2024. The study must also have a connection to the *in-situ* gelling technology and periodontitis, and it must exhibit scientific rigor and credible references. On the other hand, any study published before 2000 or in a language other than English was excluded. Furthermore, research that didn't go into enough depth about the condition, in-situ gel, or its formulations was also disqualified.

3. Common causes of periodontitis

Unlocking the mysteries of the disease requires understanding the complex interplay between specific bacterial pathogens. By studying these dynamic interactions, we can develop more effective treatments and ultimately improve the lives of those affected (**Figure 2**) (34). Bad oral health, alcoholic beverages, cigarette smoking, stress, diet, some immune diseases, and chronic diseases are all factors that can cause periodontitis. Over time, bacterial plaque, formed by gram-negative bacteria, accumulates on the supporting tissue of teeth (35).

These bacteria release enzymes such as collagenases, antigens, bacterial lipopolysaccharides, endotoxin, nitrogen trihydride, and dihydrogen sulfide. As a result, the movement of gingival crevicular fluid (GCF) in the Gingival sulcus increases, carrying a significant quantity of proteoglycans, Beta-glucuronidase, elastase, PG (prostaglandin), and neutrophil, which can lead to inflammation of the gingiva (34).

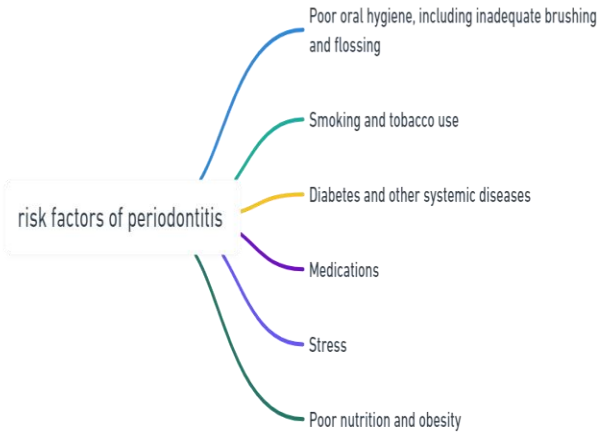

Figure 2. Periodontitis risk factors. The figure was adapted from reference (34).

The characteristics of periodontitis include inflammation in the gum, clinical attachment loss, bone loss, deep probing depths, mobility, bleeding, and pathologic migration (36). The process by which periodontitis leads to tooth loss is demonstrated in (**Figure 3**) (34).

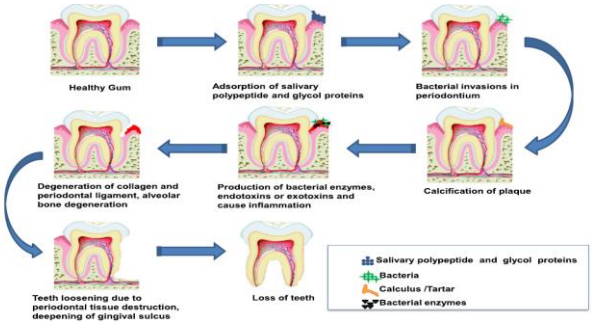

Figure 3. Mechanism of periodontitis-induced tooth loss. The figure was adapted from reference (34).

4. Current treatments of periodontitis

Patients with early or moderate periodontal disease can be treated with non-surgical methods such as scaling and root planning, which involves removing bacteria mechanically. To effectively manage periodontal disease, it is necessary to control inflammation through systemic or local administration of anti-inflammatory drugs (37). According to research, using antibiotics and antiseptics locally or systemically offers added benefits compared to only using debridement (38). The effectiveness of a treatment largely depends on how long the formulation stays in the periodontal pocket. The rate at which gingival fluid is cleared from the pocket is an essential factor that limits the drug's effectiveness. This is because it causes the active ingredient's therapeutic concentration to decrease quickly (39).

Achieving an adequate concentration of antibiotics in the areas of microbial infection, such as periodontal pockets, can be challenging when administered orally. This is a common issue with many antibiotics used (40). The frequent oral administration of the drug could cause side effects and antibiotic resistance due to its distribution in other tissues and organs, especially during long-term therapy (41). The delivery systems used for periodontitis management like fibers, stripes, biofilms, and microparticulate systems have significant drawbacks. For example, using fibers may cause discomfort in patients and result in various degrees of gingival redness after removal (15). Using a biodegradable implant in Atridox® may result in the implant accidentally dislodging from periodontal pockets, causing uncertainty regarding the drug concentration that reaches the intended site. (42). Additionally, an important matter to consider is the sudden release of medications before the implant solidifies. This could result in removing 8-95% of the drug in the beginning or immediately after the implant is inserted (43). As another example, orodispersible films are designed for oral application, which releases their contents directly into the periodontal pocket after a known time (44).

Preparing an oral drug delivery system can be challenging due to the vast adhesive nature of buccal films. However, there are limitations with electrospun nanofibers, such as poor mechanical properties, distortion, inappropriate and

uncontrolled degradation rates, patient discomfort, and drug toxicity, which restrict their application. Thus, monolithic electrospun nanofibers are deemed unsuitable for use (45). This system's significant drawbacks include using polymers that can't degrade inside the body in the form of stripes and the clinical benefits afterward treatment are temporary. On the other hand, microparticulate systems have poor retention in the periodontal pocket (46). The formulations mentioned earlier have a significant limitation: they cannot cover the entire pocket, leaving room for pathogens to occupy the pit. In-situ, gel-forming drug delivery systems comprising stimuli-sensitive polymers can be employed to overcome this drawback. These polymers undergo a solution-to-gel phase transition and cover every nook and cranny of the periodontal pocket once injected into the infected area. This transformation is due to changes in the temperature and pH of the environment (**Figure 4**) (47). The gel formulation solidifies at the temperature of the human body. As a result, it remains in the pocket for an extended period, sustaining drug delivery. This reduces the frequency of drug administration, making it easier for patients to comply with the treatment. Additionally, systemic side effects caused by antimicrobial therapy are reduced (48).

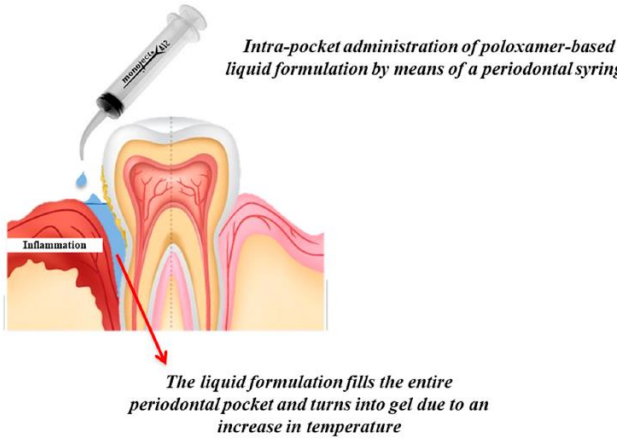

Figure 4. Rationale for the use of in-situ gelling system to treat periodontitis. The figure was adapted from reference (47).

5. *In-situ* gelling system

"In-situ" is derived from Latin and refers to something being in its innovative location or place (49). In-situ gelling systems are used to enhance the effectiveness of local or systemic delivery systems given by different routes by extending their residence duration at the site of activity (50). Many patents have been registered for in-situ gelling systems, which have been investigated for various biomedical applications, including drug delivery (12). Their potential advantages over conventional dosage forms have sparked interest in in-situ forming polymeric delivery systems. These advantages include more straightforward synthetic procedures, administered easily, decreased administration frequency, and compliance improvement. Additionally, such delivery systems promote the delivery of an accurate dose and prolong the resident's time for the drug at the application site (51). The gel can be formed in-situ due to different stimuli, such as changes in pH, temperature or solvent exchange, ionic cross-linkage, ionization, or UV irradiation (52). Innovative polymeric systems can deliver medications effectively, as these polymers undergo sol-gel transition immediately after administration. At the beginning of the 1970s, biodegradable natural and synthetic polymers were studied for sustained formulations of medications. Using biodegradable polymers in clinical applications has clear benefits. Various natural and synthetic polymers have been used to produce in-situ gel-forming drug delivery systems (53). In-situ gels are an effective solution to overcome the challenges of other local drug delivery methods. The drug is quickly absorbed because of the high blood quantity in the area, resulting in enhanced bioavailability (54).

6. Approaches used for in-situ gelling systems

In-situ gelling formulations can change from a solution to a gel-like consistency upon administration, triggered by temperature, pH, and/or ion concentration. These gels offer several advantages over conventional gels, such as accurate and consistent delivery, easy injection in liquid form, and prolonged residence on the surface due to their gelling properties (55).

There are three categories of in-situ gelling systems: ion-activated systems (e.g., gellan gum and sodium alginate), temperature-dependent systems (e.g., Pluronic, Tetronic, and polymethacrylates), and pH-triggered systems (e.g., Carbopol and cellulose acetate phthalate) (56). The phase transition process relies on a significant alteration in the water solubility of polymers with both hydrophobic and hydrophilic groups in their structure. Scientists working in the field of formulation can adjust the concentration of in-situ gelling polymers that respond to stimuli to regulate the rate and degree of gel formation, how long the gel lasts, and the speed at which drugs are released. This can be accomplished without additional organic solvents or co-polymerization agents to trigger gel formation (57).

6.1. Thermo-responsive *in-situ* gel

The concept involves the development of formulations comprising polymers that exhibit temperature-triggered sol-to-gel transitions in the range of room temperature to 37°C. These polymers can be divided into two groups: synthetic and natural. Synthetic polymers used in this concept include Poloxamer and poly (N-isopropyl acrylamide) (58). Poloxamers were the first block copolymers produced for industrial purposes, synthesized by Wyandotte Chemical Corporation in the late 1940s (59), they are commercially known by the trade names Pluronics®, Lutrol®, Kolliphor® (BASF), Antarox® (Rhodia), and Synperonics® (Croda). Commonly used poloxamers include Poloxamer 188, Poloxamer 237, Poloxamer 338, and Poloxamer 407 (60). while natural polymers include cellulose derivatives like Xyloglucan,

Hydroxypropylmethylcellulose (HPMC) and Chitosan (58),(61).

There are two categories of polymers: those that become insoluble when the temperature exceeds a certain threshold, known as the lower critical solution temperature (LCST), and those that undergo precipitation and phase change when the temperature falls below a certain threshold, known as the upper critical solution temperature (UCST). LCST polymers are called "negative temperature-sensitive polymers," such as poloxamers. On the other hand, polymers that exhibit UCST are referred to as "positive temperature-sensitive polymers," such as poly (acrylic acid) (PAA), polyacrylamide (PAAm), and poly (acrylamide-co-butyl methacrylate). As shown in (**Figure 5**) (69). When polymers exhibiting LCST are dissolved in an aqueous system, they are completely miscible at normal temperature, but their solubility decreases with increase in temperature and above a critical value, i.e., LCST, they show phase separation (62),(63).

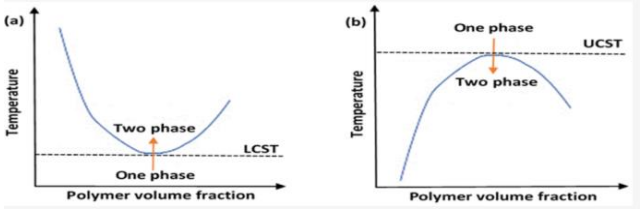

Figure 5. Phase transition phenomenon. (a) Lower critical solution temperature and (b) Upper critical solution temperature phase transition behaviors of thermo-responsive polymers in solution. The figure was adapted from reference (64).

6.2. Ion-responsive *in-situ* gel

These in-situ gelling system undergoes solution to gel conversion due to ionic stimulus. It contains an ion-sensitive polymer which undergoes gelation in the physiological environment. Gellan gum, alginate, and pectin are the most commonly used ion-sensitive gelling agents for in-situ gelling systems. They interact with cations present in the physiological fluid-like Na+, K+, Ca++, Mg++ etc, leading to cationic complexation and the formation of a 3-dimensional network structure. The periodontal pocket is abundant with cations like Ca++, when formulation contains these types of polymers, cationic complexation and polymeric interaction take place and result in solution to gel transition (65-67).

6.3 PH-responsive *in-situ* gel

pH-responsive or pH-sensitive polymers are utilized in this method for the formation of a gel. All of these polymers contain ionizable functional groups that can either accept or lose protons in response to a change in pH. Poly-electrolytes refer to a large number of ionizable groups. Hydrogels swell upon an increase in external pH, resulting in the formation of in situ gels. Some anionic groups, such as Cellulose acetate phthalate (CAP), polyethylene glycol (PEG), pseudo latexes, ploy methacrylic acid (PMC), carbomer, and its derivatives, are used as pH triggered systems. Mixtures of poly-methacrylic acid (PMA) and PEG have also been utilized as pH-sensitive systems for gelation. The majority of anionic pH-sensitive polymers are PAA (Carbopol®, Carbomer) or its derivatives (68-71).

The swelling of hydrogel changes depending on the pH level. It increases with weakly acidic (anionic) groups but decreases with weakly basic (cationic) groups (72). The protonation of these polymers results in electrostatic repulsion and the build-up of a network-like matrix, thereby causing a size expansion and swelling appearance (73).

7. Polymers commonly used for periodontal *in-situ* gelling systems

Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyepoxypropane flanked by two hydrophilic chains of polyepoxyethane, Poloxamer 407 and Poloxamer 188 are widely used in studies of drug delivery systems (74,75).

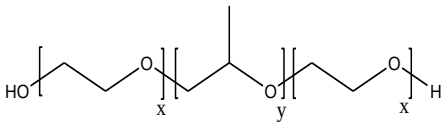

Figure 6. Poloxamer formula: x and y are the lengths of polyepoxyethane (PEO) and polyepoxypropane(PPO) chains, respectively. The figure was adapted from reference (76).

Poloxamer 407 is a non-ionic surfactant that has a wide range of applications. It is registered under the trademarks of Pluronic® F127 by BASF Laboratories and Synperonic PE/F127® by ICP Laboratories. The U.S. Food and Drug Administration (FDA) recognizes Poloxamer 407 as an "inactive ingredient" in various drug products like oral solutions, suspensions, inhalation formulations, intravenous (I.V), ophthalmic, or topical formulations (77). Poloxamer 407 is a copolymer with a molecular weight of around 12.6 kDa (POP56), and it has a polyoxyethylene content of about 70%, which adds to its hydrophilicity. Its chemical structure is shown in (**Figure 6**) (76). It is a non-ionic surfactant that is compatible with cells, body fluids, and a variety of substances, in addition to having excellent solubilizing capacity, low toxicity, and good drug release qualities (57).

Poloxamer 188 (Pluronic F-68, Flocork) is a nonionic block copolymer with polyethelyene oxide and polypropylene oxide segments arranged in an ABA structure (78). Although poloxamers have the same chemical structure, their molecular weight differs because of the difference in the number of poly (propylene oxide) and poly (ethylene oxide) units they contain (79). Hydroxypropyl methylcellulose (HPMC) is also known as Hypromellose, methyl hydroxypropyl cellulose, propylene glycol ether of methylcellulose, or methylcellulose propylene glycol ether. It has the chemical formula $C_8H_{15}O_6$-($C_{10}H_{18}O_6$)-$C_8H_{15}O_5$.

HPMC belongs to the group of cellulose ethers in which one or more hydroxyl groups in the cellulose ring have been replaced with hydroxyl groups (80). As illustrated in (**Figure 7**) (80). HPMC is a hydrophilic polymer that is soluble in deionized water. It is also biodegradable and biocompatible and has a wide range of applications in drug delivery (81). HPMC is a powder or granules that can appear white, yellowish-white or greyish-white. When it has been dried, it can absorb moisture from the air. HPMC is insoluble in hot deionized water, acetone, anhydrous ethanol, and toluene. However, it can dissolve in cold deionized water, producing a colloidal solution (82).

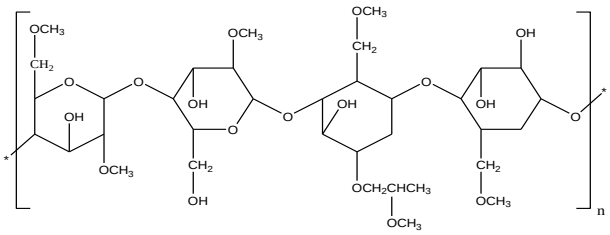

Figure 7. Chemical structure of HPMC. The figure was adapted from reference (80).

As per the European Pharmacopoeia, Carbopol® (Car934) is a polymer of acrylic acid and cross-linked poly alkyl esters of sugars or polyalcohols (83). (**Figure 8**) shows the chemical structure of Carbopol (76). This polymer comprises 56.0% to 68.0% of carboxyl (-COOH) groups calculated concerning the dried substance. Carbomers are not soluble in deionized water, but they swell, forming colloidal dispersions characterized by apparent viscosity during hydration and neutralization (84).

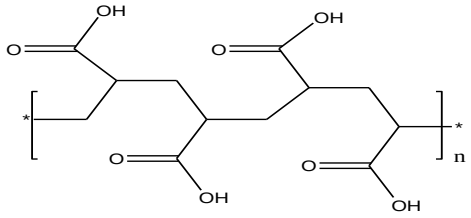

Figure 8. chemical structure of Carbopol. The figure was adapted from reference (85).

Methylcellulose (MC) is a methyl ester of cellulose (figure 9)(76) that contains 27.5- 31.5% of the methoxy groups. MC is soluble in deionized water, and its aqueous solution exhibits thermal gelation properties (80).

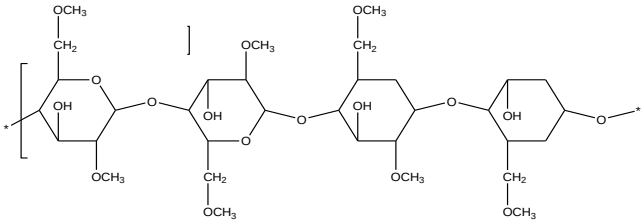

Figure 9. Chemical structure of methylcellulose. The figure was adapted from reference (80).

Gellan gum is a versatile substance that finds applications in the food, drug, and cosmetic industries. It is used as a thickening agent, gelling agent, and formulation stabilizer. The unique properties of gellan gum, such as biodegradability, biocompatibility, low toxicity, excellent thermal stability, high aqueous solubility, and good water-holding capacity, make it an ideal choice for these applications. Commercial gellan gum production involves the aerobic submerged process using the species *Sphingomonas elodea. S. paucimobilis* is utilized for industrial manufacturing. The chemical structure of high acyl gellan is shown in (**Figure. 10 A**). The high acyl groups undergo hydrolysis at high temperatures and in alkaline media to produce low acyl gellan (**Figure. 10 B**) (86).

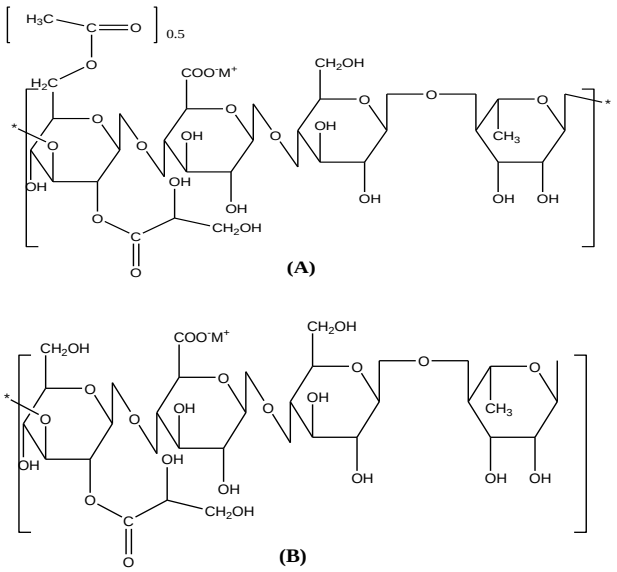

Figure 10. Gellan gum chemical structure (A) high acyl (B) low acyl. The figure was adapted from reference (86).

More rigid and brittle gels with improved thermal stability can be achieved through the deacetylation of native gellan gum and acyl substitution (87). Various textures can be gained using high and low acyl gellan gums, similar to other hydrocolloids such as locust bean gum, xanthan gum, and alginate (88). *In-situ* gels can be created by combining these two forms (89).

Chitosan, being a natural polymer, has several distinctive properties, including biocompatibility, biodegradability, antimicrobial capacity, and mucoadhesiviness. These

properties make it a fantastic option for use in biomedical or cosmetic applications. Chitin, a natural polysaccharide of the extracellular matrix, making it a suitable material for supporting cell growth, organization, and migration in tissue formation. Moreover, this attribute facilitates the smooth transportation of drugs through biological barriers (91). **Figure 11** resembles the chemical structure of chitosan (92). Chitosan chemical structure. The figure was adapted from reference (92).

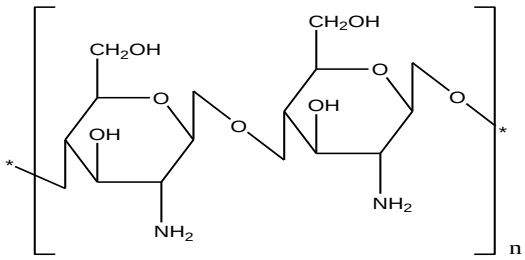

Figure11. Chitosan chemical structure. The figure was adapted from reference (92).

1. *Advantages of in-situ gelling systems*

Conventional drug delivery systems like oral, buccal, intramuscular, intravenous (93), have certain drawbacks that can be overcome by using injectable in-situ gels. These include benefits such as accurate dosing (the drug is released directly to the target site in a controlled), they can easily injected into periodontal pockets, harden to form a solid implant with longer residence time and no need to remove the empty remnants (34), increased bioavailability, reduced drug wastage, decreased frequency of administration, improved patient compliance and comfort. Furthermore, low-dose administration reduces the risk of drug accumulation, and the bio-adhesiveness of the gel allows for targeted delivery of the drug (61). Non-invasive administration of drugs can be achieved through in-situ gels, which can effectively target drugs through mucus membranes (53).

2. *Limitation of in-situ gelling system*

In-situ gelling systems, a popular drug delivery system, have certain limitations that must be considered. One of the main limitations is requiring a high level of fluids to achieve gelation (The gelation of pH and ion-sensitive in-situ systems need biological fluid for them to be fully activated) (32). Additionally, the in-situ gelling systems can degrade in their solution form, leading to stability issues due to chemical degradation (50).

Once the drug is placed inside the periodontal pocket, eating and drinking may become restricted for a few hours (94). Another limitation is the limited quantity and found in biomass after cellulose, undergoes deacetylation to obtain chitosan (90). Chitosan's structure resembles that homogeneity of drug loading into hydrogels, especially for hydrophobic drugs. Only drugs with small dose requirements can be given using in-situ gelling systems (95). Furthermore, these systems have lower mechanical strength, which may result in premature dissolution or flow away of the hydrogel from the targeted local site. It is essential to consider these limitations when designing and developing in-situ gelling systems for drug delivery (33).

3. *Various in-situ gel systems used in the treatment of periodontitis*

Three studies on different formulations were conducted to evaluate their physico-chemical, mechanical, and stability properties, as well as their in-vitro drug release and antimicrobial activity. In the first study, M. Bansal et al. (2017) created a formulation containing 10% w/v levofloxacin, 25% w/v metronidazole, 20% w/v poloxamer 407, and varying concentrations (0.5%, 1%, 1.5%, 2.0%, 2.5% w/v) of chitosan was created. This formulation was analyzed using Fourier transform infrared spectroscopy, differential scanning calorimetry, scanning electron microscope, and in-vitro antimicrobial activity against 5 bacterial strains. The optimized formulation showed good compatibility between all components, with a mucoadhesivity of the gel and sustained drug release for up to 48 hours.

The second study, P. Rahana and DSS Nair (2018) developed a formulation containing ofloxacin 0.5% w/v, 18% w/v poloxamer 407, and varying concentrations (0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35% w/v) of carbopol934. The optimized formulation was found to have a gelation temperature of 36.33±0.57°C, drug content of 95.92±0.13%, and in-vitro drug release of 72.59% at the end of 8 hours. The selected formulation also showed good antibacterial activity and stability at refrigerated temperatures for over three months.

The third study, M. Soniwala et al. (2017) developed a formulation containing Levofloxacin 0.5%, (12%,14%,16% w/v) of poloxamer 407 and (0.2%, 0.4%, 0.6% w/v) of gellan gum. The optimized formulation was found to have a gelation temperature and pH within the range of 4°- 25°C and 5.5-5.9 respectively. It also showed satisfactory results for in-vitro gelling capacity, rheology, and other physical properties. The optimized batch was formulated with 0.32%w/v of gellan gum and 14.2%w/v of poloxamer 407, based on maximum desirability, cost, and effectiveness.

All three studies aimed to develop effective antibiotic-containing formulations that can be injected into the periodontal pocket to treat bacterial infections. **Table 1**. illustrates the role of in-situ gelling systems in improving periodontitis treatment, which has been backed by studies.

Table 1. Previous studies using in-situ gelling systems for the treatment of periodontitis

Drugs	Solvents /Polymers	Result	Ref.
Heat-sensitive systems			
Moxifloxacin hydrochloride	(MC, CAR934, P407, and GG)	At 36°C, a gelling time of 102 seconds was observed in a formulation that contained 0.245% w/v of GG and 19.072% w/v of P407. Additionally, the drug was released by 98% within 9 hours.	(12)
Ornidazole and doxycycline hyclate	(CHT, P407 and P188)	The microsphere-loaded *in-situ* gel implant can be utilized to treat the periodontal pocket infection. It possesses multiple desired properties like degradable, compatible, stabile, syringabile, mucoadhesive, prolonged release, patient compliance, and price.	(96)
Levofloxacin and metronidazole	(P407, CHT)	A mucoadhesive, thermoresponsive, and controlled drug release system can be achieved with a blend of CHT 1.5% w/v and P407, which can maintain its effect for up to 48 hours.	(51)
Simvastatin	(P407, MC)	At body temperature, a gel that can be injected and has controlled drug release for up to 10 days is achieved by combining 25% P407 and 5% MC.	(97)
Curcumin	(P407 (30% w/v), CAR934 (1% w/v))	A dual response system that is pH-sensitive and thermoresponsive can be created by combining 1% w/v of CAR934 and 30% w/v of P407.	(98)
Levofloxacin	(GG, P407)	Formulation containing 0.32%w/v of gellan gum and 14.2%w/v of poloxamer 407 was consider as an optimized batch	(67)
Articaine hydrochloride	(P407, HPMC,CAR934)	The combination of articaine hydrochloride (4% w/w), P407 (20% w/w), and HPMC (0.1% w/w) can be used to achieve prolonged local anesthesia, sustained drug release, and thermoresponsive properties.	(99)
Solvent exchange systems			
Doxycycline Hyclate	(Bleached shellac, agarose, hexane, glyceryl monostearate, DMSO, NMP, PYR)	The solvent release rate of *in-situ* gels is known to last for at least seven days and follows the order of DMSO > NMP > PYR. PYR is considered the most effective solvent due to the high viscosity of bleached shellac, which significantly slows down drug release from both *in-situ* gel and *in-situ* microparticle.	(100)
Doxycycline Hyclate	(Glyceryl monostearate, DMSO, NMP, PYR)	Polymers containing *in-situ* microparticles of glyceryl monostearate and DMSO exhibit delayed thermal degradation due to their strong intermolecular forces.	(101)
Doxycycline Hyclate	(Bleached shellac, DMSO, NMP, PYR)	*In-situ* forming gels can be created by dissolving bleached shellac in DMSO, PYR, or a eutectic mixture. The eutectic mixture was found to have a higher viscosity than PYR, DMSO, and NMP. Gel formation was observed to occur at a higher velocity in DMSO than in NMP, PYR, and the eutectic mixture. However, PYR was found to have slow solvent exchange and the highest degradation rate. Preparing eutectic mixtures using needles is challenging due to their high apparent viscosity.	(102)
Doxycycline Hyclate	(Eudragid RS, N-methyl pyrrolidone, clove oil)	During in vitro testing, the exchange of solvents was slowed down with clove oil, which extended the release of doxycycline hyclate from Eudragid RS *in-situ* gel. It was observed that increasing the amount of Eudragid RS resulted in a faster liquid-to-gel transformation.	(103)
Chlorhexidine dihydrochloride	(PLGA, HPMC, NMP)	The formulation loss from gingival pockets can be reduced compared to available commercial products.	(104)
Metronidazole	(Glycerol monooleate, NMP)	Using the intra-pocket system of lyotropic liquid can improve bioavailability and reduce side effects in treating chronic periodontitis.	(105)
Doxycycline Hyclate	(Bleached shellac, NMP, DMSO, PYR, glyceryl monostearate)	Doxycycline hyclate-loaded bleached shellac *in-situ* microparticles can inhibit *P. gingivalis, S. aureus, and S. mutans*. These microparticles exhibit sustained drug release for 40 days in vitro through a Fickian diffusion mechanism.	(106)
pH-responsive systems			
Doxycycline	(α-methoxy-ω-amino-poly (ethylene glycol), DMSO)	Nanoparticles of Doxycycline mineralized were manufactured using a block copolymer, providing drug release with pH sensitivity. Calcium carbonate was used to template mineralize these nanoparticles. Due to the mineral structure, the drug release from the nanoparticles is slow at normal pH levels. However, in the acidic pH of gingiva caused by bacterial biofilm, antibiotics can be released in a controlled manner.	(107)

Curcumin	(Polyethylene glycol 400, sodium lauryl sulfate, tri-ethanol amine, P407, CAR934, propylene glycol)	The dual-response formulation in document number 1, with 1% w/v of CAR934 and 30% w/v of P407, exhibits both pH sensitivity and thermoresponsive in one system. Including 2% curcumin in the formulation results in the most satisfactory outcomes for pH, gelling temperature, and sustained drug release over extended periods.	(98)
Secnidazole, serratiopeptidase	(Alginate/HPMC, propylene glycol *in-situ* gel system)	A drug formulation that combines alginate and HPMC with secnidazole serratiopeptidase has been developed, resulting in a controlled release of the drug for over 10 hours.	(108)
Ion-activated system			
Metronidazole	(GG, thioglycolic acid)	Thiol conjugation is achieved through the esterification of GG with thioglycolic acid. As a result, gellanthioglycolic acid exhibits reduced sensitivity to cation-activated gelation. Additionally, thiolation enhances the mucoadhesive property.	(109)
Doxycycline HCL	(Sodium alginate, HPMC, mannuronic acid, guluronic acid, human serum with calcium)	The composition of the formulation includes alginate and HPMC, which function as a gel-forming agent and viscosity enhancer, respectively. The formulation is similar in composition to serum GCF and transitions from a sol to a gel phase upon mixing. Continuous drug release is achieved for 12 days using this formulation.	(110)
Photopolymerization-based system			
-	(CMCS, CHT, glycidyl methacrylate dimethyl sulfoxide)	A system was developed using a photoinitiator (420-480 nm) to decrease the gelation time of a formulation composed of biodegradable polymers.	(111)
Redox *in-situ* gel system			
-	(PEG possessing sulfanyl groups at both ends, methanol, and chloromethyl styrene)	A redox injectable gel has been developed by Saita et al. and applied to rats with periodontitis. The results showed that the drug was released steadily from the gel, oxidative damage in the periodontal area was reduced, and gingival blood flow was recovered due to the ROS scavenging activity of the redox injectable gel.	(112)

Abbreviation: P407 (Poloxamer 407), P188 (Poloxamer 188), CAR934 (Carbopol 934), MC (methylcellulose), HPMC (Hydroxypropyl Methylcellulose), GG (Gellan Gum), CHT(Chitosan), DMSO (Dimethyl sulfoxide), NMP(N-methyl pyrrolidone), PYR(2-pyrrolidone), PLGA (Poly-lactic-co-glycolic acid), CMCS (Carboxymethyl chitosan), ROS (Reactive oxygen species).

11. Conclusion

Periodontitis is a severe gum disease that causes inflammation and can lead to tooth loss. The treatment of periodontal disease can be challenging. In-situ gelling systems are drug delivery systems made of polymers that can convert from solution to gel due to different stimuli such as changes in pH, temperature, ions, or ultraviolet radiation. In-situ gels are an effective solution to overcome the challenges of other drug delivery systems and enhance bioavailability. There are three categories of in-situ gelling systems: ion-activated, temperature-dependent, and pH-triggered systems. These systems rely on a significant alteration in the water solubility of polymers with both hydrophobic and hydrophilic groups in their structure. The concentration and combination of in-situ gelling polymers can be adjusted to regulate the rate and degree of gel formation, how long the gel lasts, and the speed at which drugs are released.

In-situ drug delivery systems offer a promising platform for the treatment of periodontitis. They can inspire future advancements in treatment and innovation in in-situ gelling system design. Although in-situ gelling systems have shown great potential in preclinical studies, their effectiveness in clinical settings has yet to be evaluated. Further research is needed to refine the development of in-situ gelling systems. We are confident that, with continued progress, in-situ gelling systems will offer exciting new possibilities for the treatment of periodontitis. This will reduce patient suffering and alleviate the medical burden on society.

12. References

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نظام تكون الهلام الموقعي: طريقة أيصال واعدة لعلاج التهاب دواعم السن

الخلاصة

المقدمة: التهاب اللثة هو مرض التهابي مزمن ويمكن أن يكون شديد الخطورة ويمكن أن يؤثر على الرجال والنساء على حد سواء. وينتج عن عوامل مختلفة مثل عدم كفاية صحة الفم، والإجهاد، واستهلاك المشروبات الكحولية، وتدخين السجائر، والغذاء، وبعض الأمراض المرتبطة بالمناعة، والأمراض المزمنة. إذا تركت هذه الاضطرابات دون علاج، فإنها يمكن أن تساهم في النهاية في فقدان الأسنان وأمراض الفم الأخرى. تتوفر أنظمة توصيل مختلفة مثل الألياف والخطوط والأفلام وأنظمة الجسيمات الدقيقة لعلاج التهاب اللثة. تستخدم أنظمة توصيل الدواء في الموقع بوليمرات حساسة للمحفزات تمر بمرحلة انتقالية من المحلول إلى الهلام، مما يمكنها من تغطية الجيب بأكمله. ونتيجة لذلك، فهي أكثر فعالية في علاج التهاب اللثة من أنظمة التوصيل الأخرى. **الهدف:** تقديم لمحة عامة عن التهاب اللثة وعلاجاته وكيف يمكن لنظام التبلور الموضعي أن يعالجه بفعالية وأمان. **الطرق**: لتحقيق هذا الهدف، تم إجراء بحث منهجي واسع النطاق في قواعد بيانات مختلفة، بما في ذلك Science Direct و Springerو PubMedو ResearchGateو Google Scholar، حيث تمت مراجعة العديد من الأبحاث السابقة ذات الصلة. **الاستنتاج**: أنظمة التبلور في الموقع تشجع أنظمة توصيل الأدوية لعلاج التهاب اللثة. بسبب قدرتها على إيصال الأدوية إلى مكان الإصابة مع تقليل احتمالية حدوث آثار جانبية. هذه الأنظمة التي تحتوي على بوليمرات متوافقة حيوياً وقابلة للتحلل وقابلة للذوبان في الماء لها نتائج واعدة في تحسين علاج التهاب اللثة.

الكلمات المفتاحية: التهاب اللثة، أمراض اللثة، في الموقع، هلام بولوكسامير، كاربوبول، جيلان اللثة