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A Review on in-situ Periodontal Gel in Management of Periodontal Disease

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Abstract

Periodontal disease is a common microbial infection in adults. However, now a day it is seen that children are getting these problems also and that too in their early age. There are two types of periodontitis, namely gingivitis and periodontitis. Periodontitis is an inflammatory disease of the supporting tissues caused by a group of potential microorganisms involving anaerobes such as Treponema denticol and Porphyromonas gingivalis. However, the microaerophile Actinobacillus actinomycetemcomitans causes a rare form known as localized juvenile periodontitis. Aggressive forms of periodontitis can be localized and associated with microorganisms; therefore, treatment with antimicrobial agents is imperative. Several antibiotic therapies including tetracycline hydrochloride, doxycycline, minocycline, etc., are established in varied concentrations that inhibit the growth of pathogenic bacteria. However, the exact treatment strategies require retention of drug in the gingiva for prolonged period of time, the injectable preparations are often prescribed by dentist though they are painful. Alternative to this painful treatment has been replaced with in situ forming periodontal gel that are injected and release the active medicament for prolong duration of time for the management of gingivitis and periodontitis. The present review briefs on the formulation and evaluation of in situ forming gel using various thermosensitive polymers with an update on the recent investigations.

Keywords:- Bioadhesion, In situ, Gingivitis, Gelation, Periodontitis, PluronicF-127

1. Introduction

Periodontal disease is a collective term attributed to several pathological conditions characterized by degeneration and inflammation of the gums, periodontal ligaments, alveolar bone, and dental cementum (Fragoulis et al., 2023). It is a localized inflammatory response caused by bacterial infection of the periodontal pocket associated with subgingival plaque (Figure 1). Although bacteria is the primary cause of periodontal disease, the expression of microbial pathogenic factors alone may not be sufficient to cause the disease. Periodontal pathogens produce harmful by-products and enzymes that break extracellular matrices and host cell membranes to produce nutrients for their growth. In doing so, they initiate damage either directly or indirectly by triggering host-mediated responses that lead to self-injury. In the early phase of the disease (gingivitis), inflammation is confined to the gingivae but extends to deeper tissues, leading to gingival swelling, bleeding, and bad breath. In the late phase of the disease, the supporting collagen of the periodontium is degenerated, alveolar bone begins to resorb, and the gingival epithelium migrates along the tooth surface, forming a periodontal pocket (Kulkarni et al., 2023). This periodontal pocket provides ideal conditions for the proliferation of microorganisms, primarily gram-negative, facultative anaerobic species. Prominent among these are Bacteroides spp., Bacteroides intermedius. and Bacteroides gingivitis; fusi form organisms such as Actinobacillus actinomycetemcomitans, Wolinella recta, and Eikenella spp.; where as various Bacilli and Cocci, Spirochetes, Amoebas, and Trichomoniasis are causative microorganism (Abdulkareem et al., 2023). However, the periodontal pocket remains, and if it continues to harbor the bacteria associated with the disease, potential for a further destructive phase develops. The Disease may require extensive treatment, which if failed may lead to loss of the

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tooth. Therefore, clearance of the subgingival infection and elimination of the periodontal pocket is prioritized in the treatment of periodontitis.

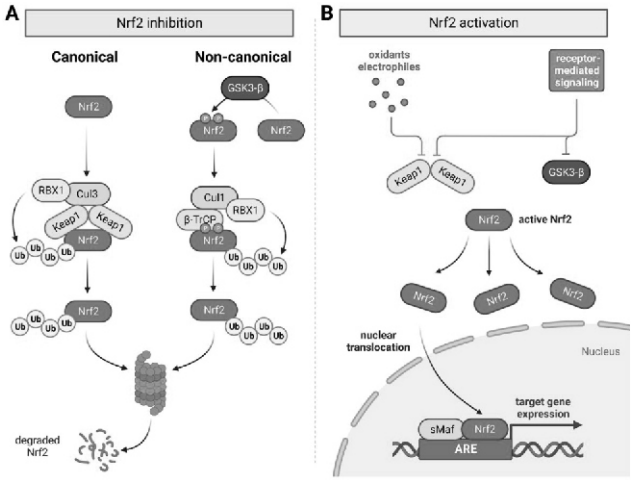

Figure 1: Dogmatic network of nuclear factor E2-realted factor activity. Process of nuclear factor E2-realted factor inhibition via canonical like ECH associated protein 1 (Keap 1) mediated and non-canonical GSK3-β/β-TrCP-mediated proteasomal degradation (A). Illustration of nuclear factor E2-realted factor activation via classical oxidant/electrophile-mediated Keap 1 inhibition and/or receptor-mediated Keap 1 as well as GSK-3β inhibition. Adapted with permission from (Fragoulis et al., 2023) under CC BY 4.0.

Periodontal diseases are a group of infections and inflammatory conditions, including gingivitis and periodontitis, which affect tooth-supporting structures (Ray, 2023). These diseases occur when bacteria from dental plaque invade surrounding tissues and accumulate at the gingival margin, which, in turn, induces an inflammatory response. The result is the formation of pockets between the gingiva and tooth, which causes gingival margin retraction and the development of an ideal environment for anaerobic bacterial growth responsible for the disease. Progression of this destructive process can lead to tooth loss. Two problems associated with many periodontal drug delivery systems are short retention time and tedious and time-consuming applications. Evidence suggests that the multitude of inflammatory and immune mediators produced by the host may cause tissue injury.

Different delivery systems based on polymers have been developed, which are able to improve the residence time of the formulation at the drug absorption site. In recent years there has been increasing interest in water-soluble thermosensitive polymers that are able to form gel after application at delivery sites. These so-called in situ gelling polymers are highly advantageous compared to 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 stronger gel, which can prolong the residence time of the active substances. Conventional treatment of periodontal disease, which consists largely of mechanical debridement of root surfaces, has a limited effect in some clinical cases with deep pockets or furcation areas that may remain untreated. Owing to these drawbacks, the use of antimicrobial agents is required as an adjunct to scaling and root planning.

Antibiotics including levofloxacin, doxycycline, moxifloxacin hydrochloride, ciprofloxacin hydrochloride, and serratiopeptidase with secniadazole are most widely used medication in these cases because it is active against periodontal pathogens. Among this metronidazole is most preferentially used that acts on anaerobic germ cells. Moreover, metronidazole prevents hydrogen production by exercising its toxic action by depriving anaerobic microorganisms of reducing equivalents that are essential for certain anabolic processes. In addition, the metabolite resulting from the reduction of the nitro group of metronidazole molecules damaged the DNA chain. This results in DNA damage in the form of loss of helical structure, probably acting as a nuclease. In situ mucoadhesive gels for periodontal diseases offer several advantages over conventional preparations, such as antimicrobial mouthwash solutions, due to prolonged duration of availability at the application site and more difficult to be removed by the saliva. This gel releases the drug exactly where the affected mucosal absorption is rapid and thus, the drug concentration is higher at the site of absorption because of the well-vascularized mucosa, they can be easily applied and have a prolonged effect. The aim of the present review is to brief on the formulation and evaluation of in situ forming gel using various thermosensitive polymers with an update on the recent investigations.

2. Etiology of periodontitis

Periodontal diseases are inflammatory conditions that affect physiological structural organs and results in infections and inflammation of the gums and bone that surround and support teeth (Figure 2). The disease may have microbiological, immunological, nutritional, hormonal, cardiovascular, or psychosomatic etiologies. Any medical condition that affects host antibacterial defense mechanisms, such as human immunodeficiency virus infection, diabetes, and neutrophil disorders, generally predispose the individual to periodontal disease. Microbial overgrowth in the form of an accumulated plaque that extends into the subgingival area of the periodontium is one of the primary reasons. This results in an inflammatory response in the adjacent tissue, initially involving the gingival tissue, and slowly progressing to the periodontium during the development of periodontitis. In early stages the condition is called gingivitis, the gums become swollen and red, and causes bleeding too. In later stage, which is more serious known as periodontitis, the gum pulls away from the tooth, bone dissolves, and the

teeth may loosen or even fall out. If untreated, it results in the loss of tooth support structures, imparting mobility to the tooth. If treatment is not initiated, irreversible loss of tooth-supporting structures can occur, resulting in tooth loss as presented in Figure 3 (Belibasakis et al., 2023). The sequential and interdependent changes to the episodic periodontitis pathogenesis is presented in Figure 4.

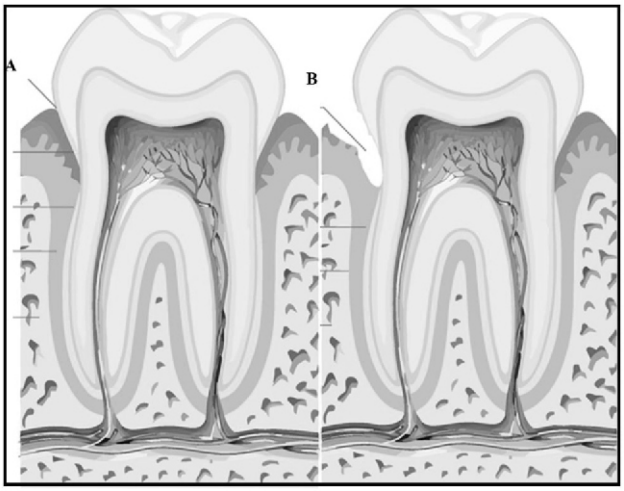

Figure 2: Pictorial presentation of healthy (A) and decayed tooth. Reproduce with permission from (Yadav et al., 2020) under CC BY 4.0.

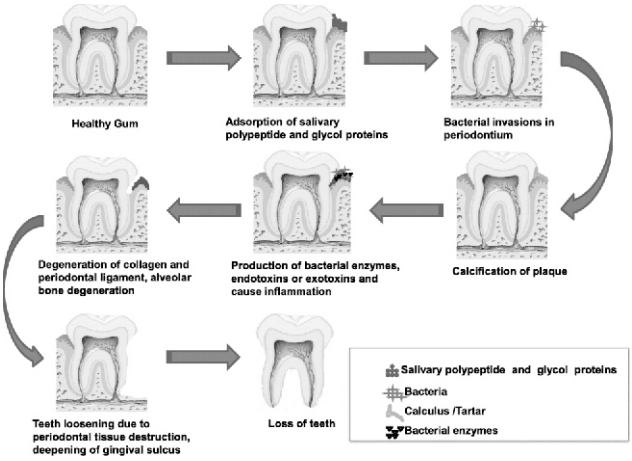

Figure 3: Systemic illustration indicating decay of healthy teeth due bacterial infection and ultimately loss. Reproduce with permission from (Yadav et al., 2020) under CC BY 4.0.

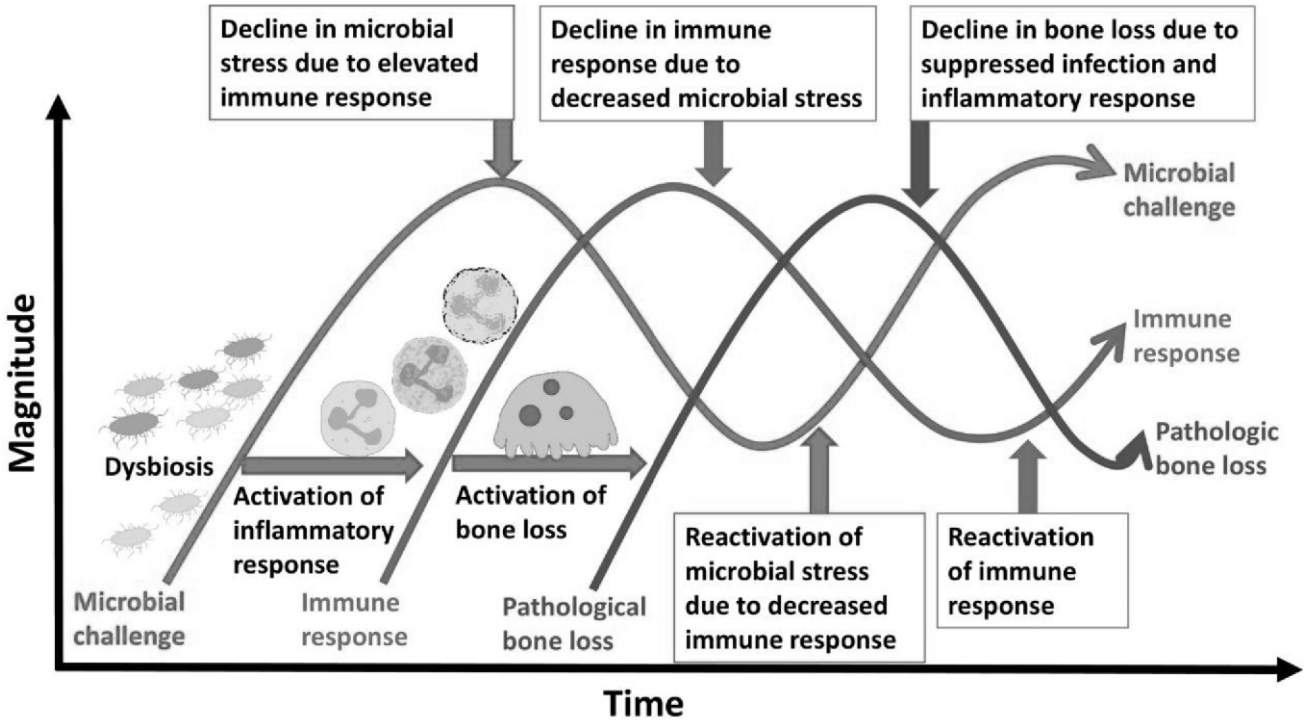

Figure 4: Illustration of sequential and inter-dependent changes to the episodic periodontitis pathogenesis model. Reproduce with permission from (Belibasakis et al., 2023) under CC BY 4.0.

3. Polymers in fabrication of in situ gels

In situ forming polymeric formulations are drug delivery systems that are in sol form before administration in the body, however once administrated, undergoes to gelation to form gel. The formation of gel depends on several factors such as temperature, pH change, presence of ions and ultraviolet irradiation, from which the drug gets released in a regulated manner. Several polymers that are commonly used in the fabrication of in situ gels are but not limited to gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly(DL-lactic acid), poly(DL-lactide-co-glycolide), and polycaprolactone. Moreover, the choice of solvents is necessary to transfer solid form of the polymer to gel form. The commonly used solvents are water, dimethylsulfoxide, N-methyl pyrrolidone, triacetin, and 2-pyrrolidone (Madan et al., 2009). The general classification of gelling polymer depending on category polymer used is presented in Table 1.

Table 1 Classification of gel

Category	Property	Polymers
Temperature sensitive	The polymer will undergo sol-gel transition on changing temperature	Pluronic F-127, F68
pH Sensitive	Polymer will swell on changing pH and give gel formation	Polyacrylic acid
Ion sensitive	Polymer when encountering ions gives gelation	Sodium alginate

3.1 Temperature sensitive gel

Temperature-sensitive hydrogels are probably the most studied class of environment-sensitive polymer systems in drug delivery research. The use of biomaterial whose transitions from sol-gel is triggered by an increase in temperature is an attractive way to approach in-situ gelation. The ideal critical temperature range for such a system is ambient and physiological temperature, such that clinical manipulation is facilitated and no external source of heat other than that of body is required to trigger gelation. A useful system should be tailorable to account for small differences in local temperature, such as encountered in appendages at the surface of skin or in the oral cavity. For convenience, temperature-sensitive hydrogels are classified as follows:

- 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 a LCST transition between the ambient and physiological temperatures are used for this purpose. One of the most extensively investigated polymers that exhibit a useful LCST transition is poly (N-isopropylacrylamide) (PNIPAAm). Poly(N-isopropylacrylamide) is a water-soluble polymer with a low LCST; however, is hydrophobic above the LCST, which results in the precipitation of PNIPAAm from the solution at the LCST. Another highly thermo-responsive polymer used is Pluronics, which is a poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) triblock co-polymer that is fluid at low temperature but forms a thermo-responsive gel when heated because of a disorder-order transition in micelle packing, making these polymers suitable for in situ gelation (Bhat et al., 2023).

Positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST); such a hydrogel contracts upon cooling below the UCST. Polymer Networks of poly (acrylic acid) (PAA) and polyacrylamide or poly (acrylamide-co-butyl methacrylate) exhibit a positive temperature dependence on swelling. The most commonly used thermo-reversible gels are prepared using poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) (Pluronics®, Tetronics®, Poloxamer). These polymers solutions are free-flowing liquid at ambient temperature and gels at body temperature. While, after injection in the body, the polymers form a stable gel. Moreover, the gel remains at the site of injection, providing absorption times ranging from less than one week to many months (Chen et al., 2023).

3.2 pH triggered systems

Another formation of an in-situ gel based on physiological stimuli is the formation of a gel induced by pH changes. All pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in the environmental pH. Polymers with several ion-stable groups are known as polyelectrolytes. The swelling of the hydrogel increases as the external pH increases in case of weakly acidic groups, however it decreases when the polymer contains weakly basic groups. Most anionic pH-sensitive polymers are based on polyacrylic acid (Carbopol) or its derivatives. Likewise, polyvinyl acetal diethyl amino acetate solutions with low viscosity at pH 4 form hydrogels under neutral pH conditions (Khan et al., 2023).

3.3 Chemically induced in situ gel systems

3.3.1 Ionic crosslinking

Polymers can undergo phase transitions in the presence of various ions. Some polysaccharides fall into the class of ion-sensitive polysaccharides. While k-

carrageenan forms rigid, brittle gels in response to a small amount of K+, while 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+. The gelation of low-methoxy pectin can be triggered by divalent cations, especially Ca2+. Similarly, alginic acid undergoes gelation in the presence of divalent/polyvalent cations Ca2+ due to its interaction with the guluronic acid block in the alginate chains (Yan et al., 2023).

3.3.2 Enzymatic cross-linking

In situ formation catalyzed by natural enzymes that have not been widely investigated but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiological conditions without the need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydrogels capable of releasing insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase swell in response to the release of entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, allowing the mixtures to be injected before gel formation (Li et al., 2023).

3.3.3 Photo-polymerization

Photopolymerization is commonly used for in situ formation of biomaterials. A solution of monomers or reactive macromolecules and initiators can be injected into a tissue site, and electromagnetic radiation is used to form a gel. Acrylate or similar polymerizable functional groups are typically used as polymerizable groups on individual monomers and macromeres because they rapidly undergo photopolymerization in the presence of a suitable photo initiator. Typically, long-wavelength ultraviolet and visible wavelengths are used for this purpose. Short-wavelength ultraviolet radiation is not used often due to limited penetration of tissue and is biologically harmful (Lindberg et al., 2021).

4. Techniques involved with evaluation of in situ gel

Several techniques are used in the characterization of gel-based formulations including physiochemical characterization of gelling polymers, compatibility analysis, sol-gel-transition temperature measurement, gelling time, gel strength, pH, viscosity, spreadability, syringeability, mucoadhesive strength, antimicrobial analysis, and drug diffusion. In this section a brief on various characterization and evaluation process involved with in situ gel forming formulation is discussed.

4.1 Sol-gel transition temperature and gelling time

Sol-gel transition temperature is referred to conversion of aqueous solution to gel form at its LCST, which usually differs for polymer to polymer and their combination used in the fabrication of gelling formulations (Medina-Esquivel et al., 2008). Similarly, the gelling time varies from polymer to polymer from several minutes to several days, even few months, depending on parameters such as temperature, polymer type, polymer concentration, cross-linker concentration, initial pH, salt type, and salt concentrations (Nguyen et al., 2012).

4.2 Gel strength and pH

The gel strength is defined as a measure of the ability of a colloidal dispersion to develop and retain a gel form based on its resistance to shear (Ahmad and Federer, 2018). The pH of the gel is usually measured using calibrated digital pH meter.

4.3 Viscosity, spreadability, syringeability and drug content

The viscosity of gel forming solutions is measured using several method, however commonly used techniques is use of digital viscometer, while spreadability is measured using roll ball process at room temperature (Ontong et al., 2020). The syringeability is generally measured using specific gauge of syringe, however commonly used gauge is 21. The drug content uniformity is measured using either UV-vis spectrophotometer or more sophisticated high performance liquid chromatography after extracting drug from gel formulation.

4.4 Mucoadhesive strength, zone of inhibition, and ex vivo diffusion

The mucoadhesive strength is measured manually using modified physical balance as represented in Figure 5 and using texture analyzer (Singh et al., 2020, Dodiya et al.). The antimicrobial zone of inhibition is tested using well-diffusion method following standard protocol (Weinstein, 2018). Moreover, the diffusion analysis tests are performed in both in vitro and ex vivo mode, either using a membrane with suitable molecular weight cut off or skin of ethically approved animals using Franz diffusion cells (Chidrawar et al., 2023).

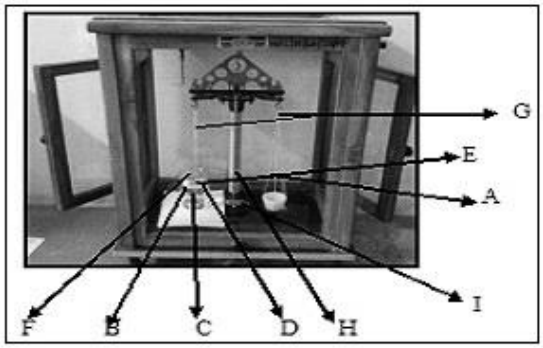

Figure 5: Modified physical balance for measurement of mucoadhesive strength. The illustrates as right pan (A), left pan (B), Teflon block (C), mucosa of

animal (D), beaker containing phosphate buffer (G), pointer (H), and scale (I).

5. Application of periodontal in situ forming gel in management of periodontal diseases

Sapra et al., developed levofloxacin in situ forming periodontal gel using statistical optimization techniques. Levofloxacin has a conventional dose of 500 mg/day, and in most cases, it does not reach the therapeutic application for local management. A formulation containing gellan gum with poloxamer 407 as a polymer incorporated with an active pharmaceutical was fabricated. The formulated composition revealed insignificant drug–polymer interactions with a gelation temperature of 40 °C and pH between 5.5 – 5.9. Moreover, viscosity was observed in the range of 600-1500 centipoise with excellent syringeability. Additionally, the tested independent variables had a significant effect on the response variables ($p<0.05$). Overall results indicated that optimized formulations containing gellan gum and poloxamer at 0.32 %w/v and 14.2% w/v, respectively, effectively regulated the release of levofloxacin for prolonged duration (Sapra et al., 2013). In another investigation, an in situ forming pocket periodontal gel of doxycycline hyclate was fabricated using poloxamer 407, chitosan, and polyethylene glycol 600, followed by statistical Box-Behnken design. Furthermore, the tested results indicated syringeability (t90%) at 1150 min with viscosity at non-physiological and physiological conditions of 512 and 5415 centipoise. Moreover, the gelation temperature was maintained at 34 °C for the optimized formulation with sustained in vitro release for 24 h, compared with the marketed gel tested. Furthermore, the optimized formulation showed an excellent mucoadhesive strength of 26 dyne/cm2 with a gel strength of 29 s using a texture analyzer. Furthermore, remarkable antimicrobial efficacy was retained by the in situ gel-forming doxycycline hyclate formulation, indicating its suitability for sustained drug delivery to treat periodontitis (Ranch et al., 2021).

Methyl cellulose-fortified atorvastatin was fabricated and evaluated by Ahmed et al., 2015 Compatibility studies indicated that the drug polymers were compatible with each other. The optimized formulation demonstrated viscosity in the range of 320-570 centipoise with pseudoplastic behavior. Moreover, gelation was achieved within 6-17 min at 29–39 °C with excellent syringeability. Based on the results of the release study, the optimized formulation showed 96.87% of drug release after 24 h. Therefore, the formulation containing 0.9% methyl cellulose was considered a potential periodontal gel-forming composition with biological attributes (Ahmed et al., 2015). Swain et al., 2019 developed moxifloxacin hydrochloride loaded in situ gel for the treatment of periodontitis. The medicated gel was fabricated using temperature-sensitive gelling polymers, such as poloxamer 407, ion-sensitive gellan gum, and pH-sensitive Carbopol 934P, using factorial design software. The results of gelation temperature and gelling time were concentration-dependent in simulated saliva with non-Newtonian and pseudoplastic flow behavior. Moreover, the diffusion investigation results indicated an augmented arrival of medication between 7-12 h and the discharge was dependent on the type of polymer used in the fabrication. Additionally, the release kinetics resulted in zero-order kinetics, indicating a controlled release of the active fortified within the gel. Furthermore, antimicrobial analysis showed efficacy against Escherichia coli and Staphylococcus aureus, indicating its suitability for the treatment of periodontal disorders (Swain et al., 2019).

Sheshala et al, fabricated poloxamer and chitosan-based in situ sol-gel-sol thermosensitive and mucoadhesive moxifloxacin periodontal gel. The formulation prepared using the cold method showed excellent sol to gel conversion at 37 °C. In addition to the sol-gel characteristics of the polymers used, mucoadhesive strength indicated adherence to the periodontal mucosa with sustained release of the incorporated actives. Antimicrobial investigations against Aggregatibacter actinomycetemcomitans and Staphylococcus mutans in agar well diffusion method showed clear zone of inhibition. Moreover, the optimized formulation containing poloxamer (21%), chitosan (2%), and β-glycerophosphate (70%) demonstrated ideal gelation temperature in range of 33 – 37 °C with regulated release for 8 h. Thus, the formulation can be suitable in reducing the dose frequency and also act as an alternative treatment to curb periodontitis (Sheshala et al., 2019). In another study, cyclodextrin-based thermosensitive in situ gel of azithromycin for periodontal delivery. The formulation was optimized using central composite design to investigate the effect of poloxamer 407 and Carbopol 934P as independent factors and percentage drug release, gelation temperature, and viscosity as dependent factors. The optimized formulation containing 18.91 % (w/v), 0.353 % (w/v) of poloxamer and Carbopol demonstrated excellent syringeability of with 21-gauge needle syringe and mucoadhesive force in range of 2352-4116 dyne/cm2. However, mucoadhesive strength of more than 10,000 dyne/cm2 reported to damage the mucosal tissue. The formulation revealed prolong release with polymer concentration dependent linearity in in vitro release profile. Further, the histopathological section for oral mucosa tested diffusion study showed no destructive effects around the microscopic structure of the oral mucosa. Furthermore, the basal membrane and epithelium layer, compared with control treatment, showed no diverse effects (Raval and Bagada, 2021).

Tiwari et al. fabricated metronidazole gel for the management of periodontal diseases using varied concentration of xanthan gum, gellan gum and guar gum, characterized, and evaluated. The formulated gel showed

pH in range of 6.16 – 6.47, with spreadability of 28.37 – 45.03 g.cm/sec and 90.01 – 99.10 (%) of drug content. Moreover, the viscosity was observed in the range of 3108.44 – 3645.47 centipoise with gelation temperature of 37 – 39 °C. Additionally, ex vivo mucoadhesive strength resulted in a mucoadhesion force of 92.54 g with adhesiveness and cohesiveness of 4.56 N/mm2 and 0.83 N/mm2, respectively indicating longer degradation of active fortified in jellified form of dosage (Tiwari et al., 2022). Aithal et al., 2018 developed in situ nanoemulgel drug delivery system of quercetin for the management periodontitis using a computational approach. Nanoemulsion containing cinnamon oil, tween 80, Carbitol®, and water fortified with quercetin incorporated within poloxamer 407 as gel base was fabricated, characterized, and evaluated. The developed nanoemulgel exhibited a remarkable release of 92.4% at the end of 6 h, compared with free quercetin in ex vivo diffusion study. Moreover, the viscosity was recorded at 30647 centipoises at room temperature. Furthermore, the simulation study to understand the gelation process demonstrated that developed nanoemulgel could be potential delivery system for clinical testing of periodontitis (Aithal et al., 2018). In another study, ciprofloxacin hydrochloride with serratiopeptidase periodontal gel was evaluated as potent broad-spectrum antibiotic against the potential periodontal bacterial infections. The gel fabricated using Pluronic F127 and Carbopol 934P followed with optimization using statistical design of experiments showed excellent syringeability and spreadability. Moreover, in vitro release study indicated > 90% of drug release in controlled regulated manner. Ultimately formulations exhibited a dual-controlled release thermoreversible periodontal sol-gel-sol formation with anti-inflammatory efficacy due to incorporation of serratiopeptidase that could be useful for treatment of periodontal inflammatory anaerobic infections too (Singh et al., 2014). Puyathorn et al., 2023 developed doxycycline hyclate loaded solvent removal-induced ibuprofen-based in situ forming gel for the management of periodontitis (Figure 6). The gel was fabricated by dissolving varied concentrations of active pharmaceuticals in dimethyl sulfoxide and N-methyl pyrrolidone. The fabricated gel demonstrated excellent physicochemical properties including pH, density, viscosity, surface tension, contact angle, water tolerance, injectability, mechanical properties, gel forming capacity (Figure 7), and drug release behavior. Moreover, the developed gel exhibited efficient antimicrobial activities against tested pathogenic microorganism (Figure 8) indicating great potential as effective bioactive drug delivery system for periodontitis treatment by localized periodontal pocket injection (Puyathorn et al., 2023). In another investigation a thermosensitive mucoadhesive periodontal in situ gel of secniadazole was fabricated for the local release and treatment of periodontitis using a cold method. The gel was developed using poloxamer 407 alone or in combination with poloxamer 188 with hydroxypropyl methyl cellulose or methyl cellulose in different grade. The optimized formulations showed gelation temperature, gel strength, mucoadhesive force strength, and in vitro release of 32 - 33 °C, 1.5-2 h, 17.1 – 23.4 dyne/cm2, and 98.2-100 %, respectively with excellent compatibility between drug an polymer indicating suitability for the management of periodontitis (Dheyaa A. Raheema, 2022).

Maddeppungeng and co-worker developed a thermosensitive in situ gel of metronidazole microparticles for intra-pocket administration using polycaprolactone or chitosan as an alternative in periodontitis management. The study assessed for antimicrobial efficacy against Staphylococcus aureus and Escherichia coli suggested potential ability to kill the pathogens at tested concentrations. Moreover, ex vivo results suggested insignificant changes in biofilm quantity, bacterial counts, and metabolic activity in biofilm suggesting improved patient compliance (Maddeppungeng et al., 2024). In another study by Liu and co-worker, developed in situ curcumin/zinc oxide hydrogel for effective treatment of periodontitis demonstrated excellent activity against P. gingivalis with good biocompatibility (Liu et al., 2024). Similarly, an injectable gel-based on photo-cross-linkable hyaluronic acid and mesoporous bioactive glass nanoparticles for periodontitis management developed by Hu and co-worker demonstrated an effective inhibition of Streptococcus mutans and the expression of pro-inflammatory factors (IL-6 and TNF-α) when tested on macrophages. Moreover, the study suggested significant upregulation of MC3T3-E1 cells expression for osteogenic-related genes such as ALP, Runx2, OPN, and osterix, indicating the use of formulation for guided bone regeneration treatment of irregular periodontal defects (Hu et al., 2024). Furthermore, in a randomized controlled trial with microbiological analysis for testing the efficacy of locally delivered hyaluronic acid gel as an adjunctive to non-surgical management of stage II or stage II periodontitis. The analysis on statistical results showed advancement in both groups (intervention group with scaling and root surface debridement with local application of 0.2% test formulation and group that had scaling and root surface debridement only) after 1 and 3 months follow up. Additionally, there was an insignificant difference regarding microbiological analysis between 2 groups after 3 months, suggesting that the application of 0.2% test formulation once in patients with stage II or III periodontitis had limited effect regarding clinical and microbiological analysis (EL-EMAM et al., 2024).

Recent advancements in periodontal disease management

Recent advancement in the management of periodontal disease have increasingly incorporated additive manufacturing technologies, enhancing treatment efficacy and patient outcomes (EL- Vyas et al., 2024;

Ashique et al., 2024; Li et al., 2024; Gu et al., 2024; Li et al., 2024; EI-Nablaway et al., 2024; Al-Dabbagh et al., 2024; Deshmukh et al., 2024). Some of extensively reports on consumer centric approach for periodontal disease management is presented below.

Three-dimensional printing of custom implants and guides: additive manufacturing allows for the development of patient-specific dental implants and surgical guides. This customization improves the precision of procedures such as guided tissue regeneration and implant placement, which are crucial in treating advanced periodontal disease. Custom-fit implants can enhance osseointegration and overall treatment success by ensuring better alignment with the patients anatomical structures.

Bioprinting for tissue engineering: innovative approaches in bioprinting are being explored to regenerate periodontal tissues. This method involves printing living cells and biomaterials to develop scaffolds that can support the growth of new gum and bone tissue. Such advancements aim to restore the structural integrity of the periodontium, potentially reversing damage caused by periodontal disease.

Enhance diagnostic tools: additive manufacturing has also improved diagnostic capabilities through the development of advances intraoral sensors and imaging devices. These tools provide high-resolution images that aid in the early detection of periodontal disease, allowing for timely and more effective interventions.

Integration with other technology: The combination of additive manufacturing with other innovative treatments, such as laser therapy and platelet-rich plasma therapy, is being researched. These integrative approaches aim to enhance tissue regeneration and promote healing in periodontal patients, ultimately improving long-term outcomes.

Research and development: ongoing research is focused on the use of three-dimensional printed scaffolds that can deliver therapeutic agents directly to periodontal tissues. This targeted delivery system aims to reduce inflammation and promote healing by utilizing growth factors and anti-inflammatory agents, addressing the limitations of traditional systemic therapies.

These advancements highlight a significant shift towards more personalized and effective treatment strategies in periodontal disease management, driven by capabilities of additive manufacturing and related technologies.

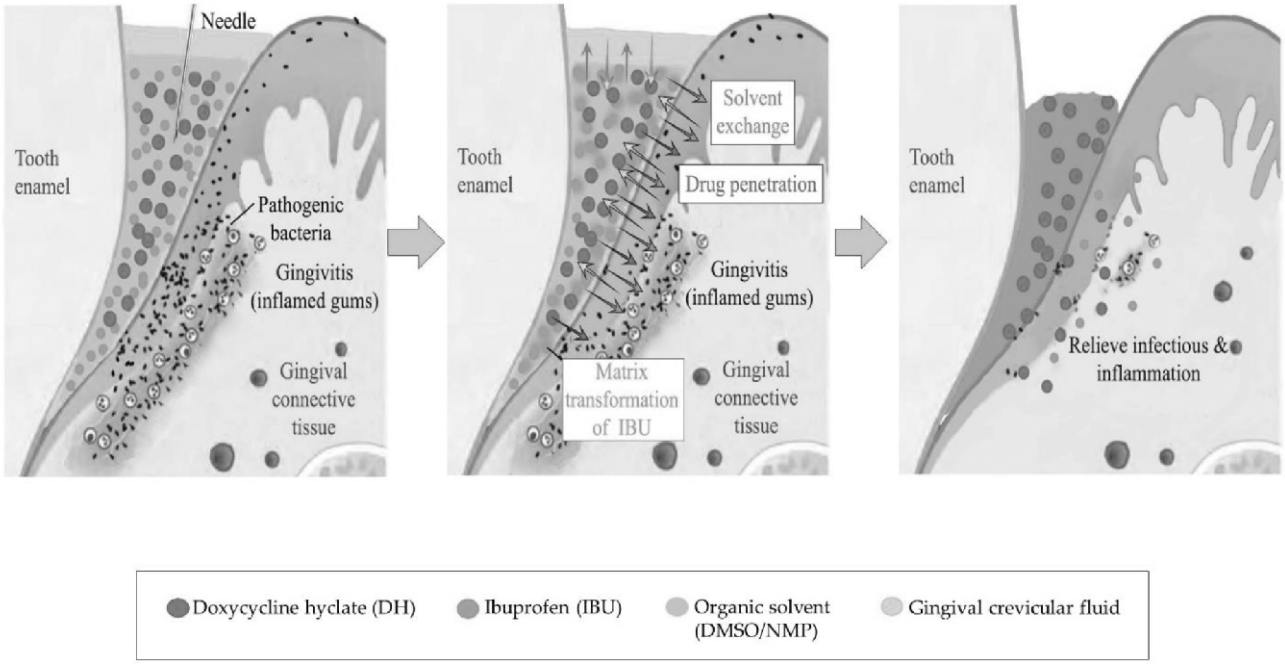

Figure 6: Illustration demonstrates permeation of active pharmaceutical from in situ gel with significant reduction in the growth of pathogenic bacteria and inflammation in gingivitis. Adapted with permission from (Puyathorn et al., 2023) under CCBY 4.0.

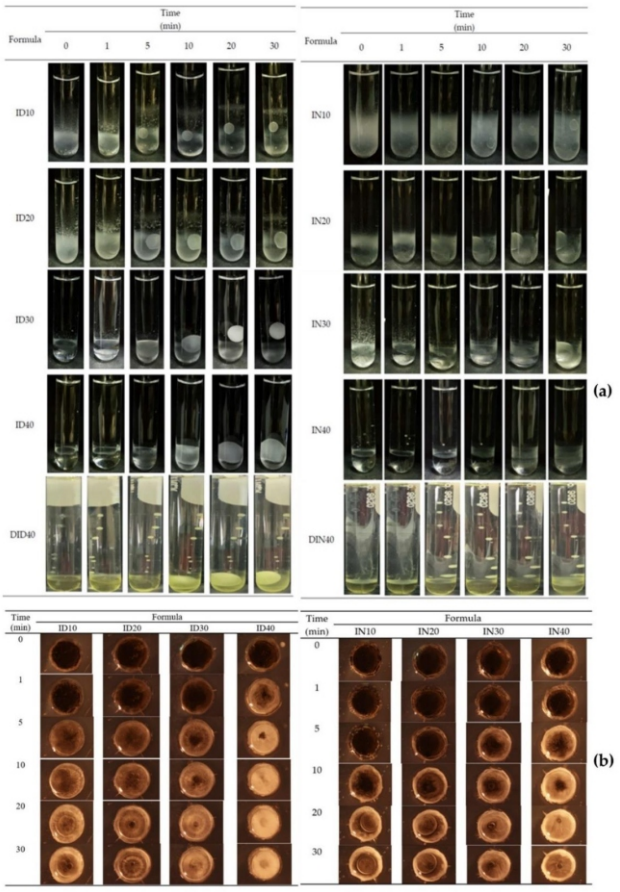

Figure 7: In vitro matrix formation behavior of active incorporated within the gel (a), cross-sectional illustration of gel formation in presence of various solvent tested within agarose well using microscope at 2X. Adapted with permission from (Puyathorn et al., 2023) under CC BY 4.0

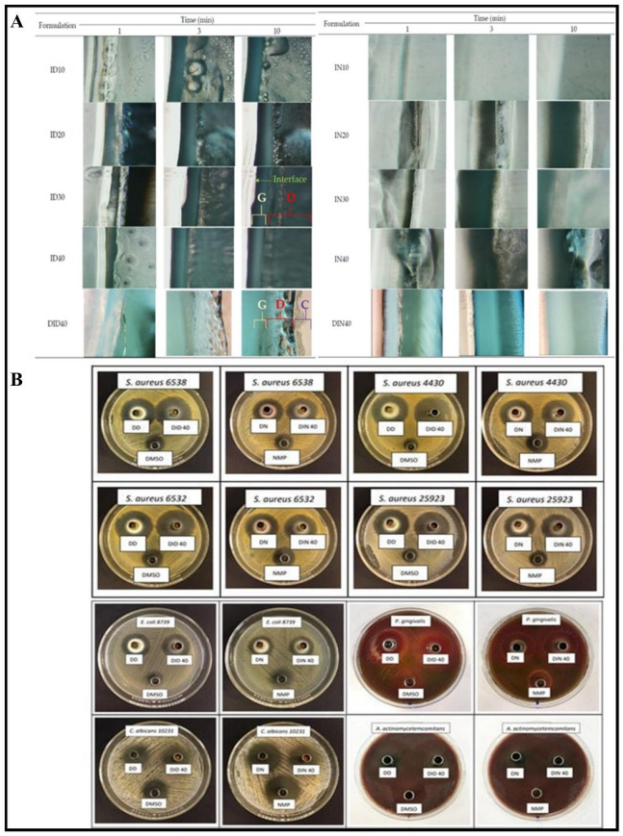

Figure 8: Boundary formation by matrix gel formulation at the interface of the aqueous phase and in situ forming gel system during the initial testing at 100X under inverted microscope (A). The figure shows that gel formed three different layers namely gel formation represented by 'G' the droplet fluctuation layer represented by 'D' and the clear in situ gel formation represented by 'C'. The initial phase of gel transformation presented only a thin D layer between the interface and the C layer. As the time lapsed, the D layer expanded to the C layer, and the G layer formed represented by gel around the interface. Zone of inhibition for drug loaded based on in situ system against Staphylococcus aureus (ATCC 6538, 6532, and 25923), Staphylococcus aureus (MSRA: ATCC4430), Escherichia coli (ATCC 8739), Candida albicans (ATCC 10231), Porphyromonas gingivalis (ATCC 33277), and Actinomycetemcomitans (ATCC 29522) (B).

Conclusion

In this review, we highlighted the relevance of in situ gel forming formulation in the treatment of gingivitis and periodontitis, which are microbial diseases that lead to inflammation in the tooth supporting tissues of the oral cavity. The periodontal diseases are initiated by oral inflammation induced by bacterial infections followed with biofilm formation. Several oral drug delivery systems fortified with antibiotics are available to treat such bacterial infection; however due to low solubility, gastric retention time the therapeutic effects are no longer effective as local dosage form. In situ periodontal formulation brought a revolution in the management of gingivitis and periodontitis due to availability of thermo-responsive polymers that change to gel form with change in temperature. However, further clinical research is required to be done and encouraged to prove the in situ gel formulation efficacy

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