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A PERCEPTIVE VIEW ON IN SITU GEL FOR THE TREATMENT OF PERIODONTITIS

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ABSTRACT

Periodontitis is an inflammatory disease of the tooth-supporting tissues caused by specific microorganisms. The idea of treating localised problem sites with local drug delivery seems appealing because the antimicrobial agent is delivered within periodontal pockets and the therapy is directed at specific pathogenic microorganisms. A novel in situ forming gel is introduced at the site, with the potential to overcome one of the main practical challenges associated with the treatment of local periodontitis: partial adhesion to the surrounding tissue, resulting in the accidental removal of at least parts of the implants from the patient's pockets. For the treatment of localised forms of periodontal destruction, controlled release antimicrobial agents should be considered as an adjunct to mechanical debridement. Local delivery of an in situ gelling system to periodontal pockets has the advantage of putting more drugs at the target site while minimising total body exposure to the drug The most appropriate type of formulation for the treatment of periodontitis has been found to be oral in situ gel because it delivers the drug locally, allowing the dose to be reduced while also reducing toxicity. In situ gel formation can be caused by a variety of mechanisms, including solvent exchange, UV irradiation, ionic cross-linking, pH change, and temperature modulation.Here we highlight about the methods of oral in situ hydrogel, polymers used in the preparation and also examines periodontitis pathogenesis as well as its diagnosis and treatment.

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INTRODUCTION

The first stage of periodontitis is gingival infection, which is mostly brought on by the presence of gram-negative bacteria in the deeper gingival sulcus and later periodontal pockets[1]. Periodontitis develops as the disease proceeds from gingivitis. Gum tissue, periodontal ligaments, alveolar bone, and dental cementum all experience deterioration and inflammation during this condition. The primary cause of periodontitis is bacteria. Periodontal disease is brought on by bacterial infections as well as hereditary and environmental factors. Around the tooth root surface, a bacterial coating forms first. In order to produce nutrition for their growth, periodontal infections produce enzymes and toxic by-products that rupture host cell membranes and extracellular matrix. The periodontal pathogens do this by inciting host-mediated reactions that result in destruction[2].

This disease can be classified as gingivitis when inflammation is localized to the gingiva, and periodontitis, when extends to deeper tissues. In later stages of the disease ligaments of periodontium are disintegrated, reabsorption of alveolar bone occurs and gingival epithelium migrates along with the tooth surface forming a periodontal pocket. These pockets provide ideal environment for growth and proliferation of pathogenic bacteria[3].

If the periodontal pocket continues to harbor the microorganism associated with the disease, it may lead to further destructive phase. Then the disease may require extensive treatment. Failure of the treatment may lead to tooth loss[4]. Severe periodontitis may develop in any age group but it is commonly found in 5-20% of most adult population worldwide[5].

Periodontitis is initiated by a limited number of periodontal pathogens in the complex dental biofilm. Several bacterial species can colonize sub gingival microflora but only a few species have been associated with the development of disease. These bacterial strains are called as periodontal pathogens[6].

Most of the periodontal pathogens are anaerobes, but facultative aerobes, capnophiles and microaerophiles can also harbor biofilm. A deepened periodontal pocket is dominated by Gram negative anaerobic rods and spirochetes. Porphyromonasgingivalis and Aggeregatibacteractinomycetemomitans are the main cause of adult periodontitis. In addition, Prevotella intermedia, Bacteroidesforsythus, Peptostreptococcus micros and Fusobacteriumnucleatum have been strongly connected with the progression of adult periodontitis[7,8].

Risk factors of periodontal disease may be modifiable or non-modifiable. Modifiable risk factors are usually behavioural or environmental in nature whereas non-modifiable risk factors are usually inherent to the individual and therefore not easily changed. Modifiable risk factors include smoking, diabetes mellitus, stress and microorganisms. Non-modifiable risk factors include genetic factors, host response, osteoporosis, and several systemic diseases such as Chediak-Higashi syndrome, cyclic neutropenia, lazy leukocyte syndrome, agranulocytosis, leukocyte adhesion deficiency, Down syndrome and Papillon Lefevre syndrome and aging[9].

Advances in the understanding of the aetiology, microbiology and epidemiology of the periodontal pocket flora have transformed the therapeutic strategies for the management of periodontal disease progression. The value of administering antimicrobial agents is an inexpensive and rapid means of increasing mechanical periodontal debridement is worth consideration. The therapeutic success or failure depends not only on the antimicrobial activity of the agent but also on the location of the infection, carrier systems and route of administration. Current approaches to periodontal therapy target the areas to provide constructive treatment for periodontal disease [10].

Dental caries (tooth decay), severe gum disease, tooth loss, and oral cancers are the most common oral diseases. Untreated dental caries is the most common disease in the world, affecting an estimated 2.5 billion people. Severe gum disease, a leading cause of total tooth loss, is thought to affect one billion people worldwide [11].

Periodontal diseases are common both in developed and developing countries and affect about 20-50% of global population · High prevalence of periodontal disease in adolescents, adults and older individuals makes it a public health concern. Periodontal disease is likely to cause 19% increase in the threat of cardiovascular disease, and this increase in relative risk reaches to 44% among individuals above 65 years. Type 2 diabetic individuals with serious form of periodontal disease have 3.2 times greater fatality risk compared with individuals with no or mild periodontitis. Periodontitis is related to maternal infection, premature delivery, low birth weight, and preclampsia. Oral disease prevention strategies should be incorporated in chronic systemic disease preventive initiatives to diminish the burden of disease in populations. The decrease in the incidence and prevalence of periodontal disease can reduce its associated systemic diseases and can also minimize their financial impact in the health-care systems [12].

Systemic antibiotics, on the other hand, are recommended for the treatment of rapidly progressing or refractory Periodontitis. For the treatment of periodontal disease, various synthetic antibacterial and antibiotic agents such as tinidazole, metronidazole, ciprofloxacin, tetracycline, doxycycline etc. were used.Multiple systemic antibiotic doses have revealed several drawbacks, including: insufficient antibiotic concentration at the site of the periodontal pocket; rapid decline of plasma antibiotic concentration to sub therapeutic levels; microbial resistance development; and high peak-plasma antibiotic concentrations. This could result in side effects. These obvious drawbacks have piqued the interest of researchers in developing novel intra-pocket drug delivery systems for the treatment of periodontal diseases. The periodontal pocket provides a natural reservoir, which is easily accessible for the insertion of a delivery device.Local application is one method of targeting a drug to a specific site in order to avoid the side effects and discomfort associated with conventional therapy. To prolong the therapeutic levels of the drug at the site, however, a device for sustained and prolonged drug release at the site is required. Of the existing local drug devices in situ gel is the best option for the intended effect. For the treatment of periodontal disease, various synthetic antibacterial and antibiotic agents such as tinidazole, metronidazole, ciprofloxacin, tetracycline, doxycycline, and others were tried in the form of local controlled devices [2,10].

PATHOGENESIS OF PERIODONTAL DISEASE

A complex biofilm, or colonisation of bacteria surrounded by a protective matrix, is what is known as dental plaque. The extracellular polysaccharide and glycoproteins in this matrix provide the dental biofilm's bacteria with a safe haven [13]. This element of the dental biofilm increases its resistance to antimicrobial treatments by 1000–1500 times [14]. A large number of nutrients are distributed and metabolic waste is excreted by the biofilm's many circulatory channels. A kind of communication used by the bacterial microcolonies that make up the dental biofilm is called "quorum sensing " [15]. The quantity of "autoinducers," which are chemicals released by germs, aids in controlling the expression of bacterial genes [15]. The biofilm contains a variety of microenvironments due to its varying pH levels and metabolites. The ecosystem can support a range of bacteria living in the same dental plaque [13].

"Acquired pellicle" refers to the first layer of dental plaque that is placed on the surface of teeth [16]. This layer is created just seconds after tooth surfaces are exposed, and it is then followed by the adhesion of the first biofilm colonisers. The most frequent colonisers are gram-positive, facultative Streptococcus and Actinomyces species [16]. Theproline-rich proteins of the pellicle are bound by the "adhesin receptors" on the surface of primary colonisers. This binding causes the "cryptitope" receptor sites to become visible, which in turn causes coaggregation. [17]. Dental plaque builds up gradually, layer by layer, causing an oxygen shortage that finally encourages the colonisation of anaerobic bacteria [18].Fusobacterium species serve as the link between primary and secondary invaders [18]. Gingivitis progresses to periodontitis as these aerobic settings gradually change to anaerobic conditions. In a study, Socransky et al. classified the microorganisms into microbial complexes according to their hue [19]. Periodontal disease is intricately linked to red and orange complexes of bacteria that are seen in the subgingival region [20].

The host gradually mounts a traditional innate immune response in response to the bacterial infection [21]. The reaction consists of neutrophil migration to the site of inflammation along with indications of acute inflammation such as increased gingival redness, bleeding, and swollen gums. The body's primary host cells are also turned on by the innate immunity, which also sets off the adaptive immunity and gets the body ready for defence against bacterial infection [21]. Additionally, innate immunity causes the host cell to differentiate into more specialised cells, which in turn raises the levels of pro-inflammatory mediators such as interleukin-1beta, prostaglandins, and tumour necrosis factor [21]. The cascade is set off, and as a result, certain T and B cells are activated, bringing adaptive immunity into motion. The function of B and T cells has been studied. There is evidence to support the participation of B and T cells in the activation of RANK (Receptor Activator of Nuclear Factor-kB), which induces osteoclast activation and bone loss [22].

EPIDEMOLOGY

Because it depends on the host reaction, not all cases of gingivitis proceed into cases of periodontitis [23]. Periodontitis can be broadly divided into aggressive and chronic types. Chronic periodontitis (CP) cases are characterised by an abundance of plaque and calculus [24]. While the familial aggregation of the illness and greater quantity of periodontal damage with little local variables are the defining characteristics of aggressive periodontitis (AgP) [25]. Local aggressive periodontitis (LAP) and global aggressive periodontitis are other classifications for AgP. (GAP). Susin et al epidemiological analysis indicates that differences in ethnicity and geographic location have an impact on the prevalence of LAP [26]. According to estimates, it affects African Americans at 2.6%, Africans at 1 to 5%, Asians at 0.2%, North Americans at 0.5 to 1%, and South Americans at 0.3 to 2% [26]. Globally, the prevalence of GAP is 0.13% while that of LAP is less than 1% [26]. Comparatively to wealthy nations, chronic periodontitis is more common in underdeveloped nations [27]. The National Health and Nutrition Examination Survey III (NHANES III) found that gingival and periodontal disease affected 50% of the adult population in the United States [28].

HISTOPATHOLOGY

A reversible process without any bone or periodontal support loss, gingivitis is the first stage of the body's reaction to local factors present in the oral cavity [29,30].According to histopathology, ulcerations in the sulcular epithelium are caused by the destruction of collagen fibres within the lamina propria [31]. Page et al. claim that gingivitis has three histological stages: the initial lesion, the early lesion, and the established lesion [31]. Different cells distinguishing the transition between these stages are used to mark these lesions. By moving from the established stage to the advanced stage, more inflammatory alterations in the gingiva cause the onset of periodontal disease [31]. Collagen fibres are destroyed as a result of the lateral and apical migration of inflammation from epithelium to connective tissue. The clinical manifestation of this degradation of collagen fibres is "attachment loss," which denotes the transition from gingivitis to periodontitis. Osteoclast cell activation causes bone resorption to begin gradually, which causes tooth loss over time [31].

CLASSIFICATION OF PERIODONTAL DISEASE

Periodontal disease can be classified based on its extent and severity [32].

1. Gingival disease.
a) Plaque induced
b) Non-plaque induced
2. Chronic periodontitis.
a) Localized
b) Generalized
3. Aggressive periodontitis.
a) Localized
b) Generalized
4. Periodontitis as a manifestation of systemic disease.
5. Necrotizing periodontal disease.
6. Periodontal Abscess.

Gingivitis

A non-destructive and reversible form of periodontal disease is gingival disease. Clinical symptoms include itchiness, gum inflammation, more frequent gingival bleeding, and red or bluish gingiva. Lack of good oral hygiene is a common cause of gingivitis. Periodontitis can develop if the root causes are not treated, which could result in the loss of attachment surrounding the teeth.

Gum inflammation caused by bacteria along the gingival border, which may eventually expand to the entire gingiva, is known as dental plaque-induced gingivitis. It is solely related to plaque and is modifiable by drugs or starvation. At the base of the teeth, close to the gums, plaque can harden into calculus or tartar if it is not sufficiently cleared. Around the tooth's root, plaque and tartar will irritate and inflame the gums.

Gingivitis caused by infections such as bacteria, viruses, and fungi rather than plaque. It may also result from hereditary issues, injuries, etc. Microbes like Streptococcus, Treponema pallidum, Neisseria gonorrhoeae, and others produce gingival disease that is bacterial in nature. The most significant herpes simplex virus (HSV) types 1 and 2 and varicella zoster virus are linked to viral gum disorders [33,34].

Chronic Periodontitis

Although it is infrequently observed in kids, it is the most prevalent type of periodontitis in adults. It is characterised by persistent periodontal tissue inflammation brought on by a large buildup of tooth plaque. Inflammation inside the tooth's supporting tissues, increasing attachment loss, and bone loss that results in pocket formation are all clinical indications.

According to its extension, it can also be categorised as:

• Localized, if fewer than 30% of the affected sites.
• Generalized, if the problem affects more than 30% of the sites.

According to its intensity, the illness can be divided into:

• Mild: CAL(clinical attachment loss) of 1-2 mm or less indicates mild attachment loss.
• Moderate: when the CAL ranges from 3 to 4 mm.
• Severe: CAL of 5 mm or greater.

Signs of inflammation are frequently different depending on the patient's control of plaque. Teeth may move around or migrate as the illness worsens [33,34].

Aggressive Periodontitis

It is a form of periodontal disease, and its hallmarks include fast bone deterioration and attachment loss, a positive family history, and the presence of periodontitis in otherwise clinically healthy patients.

Localized aggressive periodontitis and generalised aggressive periodontitis are two varieties of this condition.

1.Localized

It typically manifests during puberty and has a strong immune response to infection-causing substances. First molar or incisor attachment loss was the only one present.

2. Generalised

Although it can occur at earlier ages, it often appears around the age of 30. In addition to initial incisors and molars, it is distinguished by extensive interproximal attachment loss that affects at least three permanent teeth [33,34].

Periodontitis As A Manifestation Of Systemic Disease

Systemic diseases that affect inflammatory responses, immune functions and tissue organization can modify the onset and progression of all forms of periodontal disease. This classification includes various hematological disorders such as leukaemia and acquired neutropenia, various genetic disorders such as Down syndrome, familial and cyclic neutropenia etc. Diseases such as diabetes and HIV are considered as the modifiers of both chronic and aggressive periodontitis [33,34].

Necrotizing Periodontal Disease

This category includes both necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP). Both NUG and NUP related to decreased systemic resistance to bacterial infection and may only differ in terms of the tissue affected, with NUP extending in to periodontal attachment loss. Stress and smoking tobacco are common predisposing factors for necrotizing periodontal disease.

Necrotizing ulcerative gingivitis tends to recurrent if predisposing factors is not eliminated and progresses to necrotizing ulcerative periodontitis, in some cases causing severe destruction of periodontal tissues.

Gingival erythema and edema, loss of papillary tissues with punched out crater ulcers and spread the ulceration to the marginal tissue with obvious bleeding is seen in some cases [33,34].

Periodontal Abscess

Periodontal abscess was added as a separate category. In most cases periodontal abscess formation considers the acute exacerbation of a pre-existing periodontal pocket. It may be more correctly called as an acute periodontitis. Abscesses may take place because of other causes such as foreign body impaction, trauma, including occlusal trauma causing vertical and horizontal root fractures or cemental tears [33,34].

Table No.1 Microorganisms associated with endodontal and periodontal infections [35].

AEROBIC AND FACULTATIVE ANAEROBIC SPECIES	ANAEROBIC SPECIES
Gram negative rod	**Gram positive cocci**
Peptostreptococcusgingivalis	Peptostreptococcusspp
	Peptostreptococcus miller
Gram positive cocci	
Streptococcus spp	**Gram negative bacilli**
Streptococcus mutans group	Veillonellaspp
Streptococcus milleri group	
Beta-hemolytic streptococci	**Gram positive bacilli**
	Peptostreptococcus micros
Gram positive bacilli	Actinomycesspp
Lactobacillus spp	Eubacteriumspp
Rothiadentocariosa	Propionibacteriumspp
	Lactobacillus spp
Gram negative cocco-bacilli	
Aggregatibacteractinomycetemcomitans	Spirochetes
Actinobacillusactinomycetemcomitans	*Treponemadenticola*
Campylobacter spp	*Treonemasocranski*
Capnocytophagaspp	
Eikenellaaspp	**Gram negative bacilli**
Tannerellaforsythensis	*Prevotella intermedia*
	Porphyromonasspp
	Aerophilic Gram negative rods
	Capnocytophaga species

TREATMENT OF PERIODONTAL DISEASE

Periodontal treatment depends on the type and severity of gum disease. Aim of the treatment is to prevent further progression of the disease, reduce the symptoms, to rebuild the lost tissues and to support the patients in maintaining a healthy periodontium. Periodontal treatment uses various nonsurgical and surgical methods to achieve these goals [36,37].

A.Surgical Treatment Of Periodontitis

Compared with nonsurgical treatment taken to improve deep untreated pockets, surgical treatment has exhibited a better performance in terms of pocket closure and preservation of teeth. However, surgery should be limited to periodontal pockets deeper than 5 mm to avoid mechanical damage to the periodontium. Differences in outcome of the various types of surgical and nonsurgical treatments tend to disappear over time with individual's oral hygiene [38,39].

When non-surgical treatment does not restore the healthy gums, surgery may be needed. The following are different types of surgical treatment for periodontal disease:

1) Soft tissue grafts:

Soft tissue grafts increases gum tissue thickness and covers exposed roots where gum is absent due to excessive gingival recession. In this procedure gum tissue taken from palate to augment tissue thickness and cover the exposed root. Soft tissue graft can help to inhibit further recession. This procedure can also reduce tooth sensitivity, covers exposed roots and improve esthetics of smile [39].

2) Frenotomy:

It is the surgical removal of a frenum in the mouth. A frenum is a fold of tissue that runs from the movable lip or cheek to the gum. Frenotomy is indicated when a frenum is positioned in such a way as to intervene with the normal alignment of teeth or results in pulling away of the gum from the tooth surface lead to recession [39].

3) Gingivectomy:

Since the bacteria that causes periodontal disease breed in the deepened pockets between the gum and the tooth, dentists may attempt to eliminate the area in which these bacteria can grow with a gingivectomy. In a gingivectomy, the periodontist will trim the unhealthy gum in order to reduce the pocket size. As a result, the bacteria will no longer have a suitable environment in which to grow, and healthy gum tissue can begin to grow back [39].

B. Nonsurgical approaches

Nonsurgical therapy aims to eliminate living bacteria present in both microbial and calcified biofilms from the tooth surface and adjacent soft tissues. Complete elimination of such pathogenic microorganisms is not possible. However, a reduction in the bacterial load can be achieved, which may reduce inflammation of the periodontium and leads to beneficial clinical changes. In addition, this therapy aims to create an environment in which the patient can more effectively prevent pathogenic microbial recolonization by personal oral hygiene methods. The various methods used in nonsurgical therapy, such supragingival biofilm control, subgingival instrumentation and adjunctive pharmacological therapy [40].

1) Supragingival biofilm control

Supragingival plaque can be controlled by self-oral hygiene measures and professional removal of plaque and calculus. Plaque that can cause periodontal disease can only remove with professional cleaning. Poor oral hygiene results in development of high rate of dental plaque which may lead to lower healing capability and prevent a successful nonsurgical treatment.
Mechanical plaque removal. is performed with tooth brushes. As an adjunctive to mechanical plaque control chemical products such as tooth pastes and mouth rinses are used [41].

2) Subgingival instrumentation

It is divided into three distinct procedures; debridement, scaling and root planing. Debridement is the removal of subgingival plaque and is equivalent to supragingival polishing. Scaling is aimed to remove plaque, calculus and stains from the crown and root surfaces. Root planing is performed to remove diseased root cementum or surface dentin containing calculus, toxins or microorganisms. Gingival bleeding can be reduced by removal of plaque and subgingival debris [40,41].

3) Adjunctive pharmacological therapy

Mechanical therapy has limited effect on some periodontal pathogens and fails to remove microbial species present in the nondental biofilm. Moreover, mechanical debridement can cause unpleasant side effects such as loss of tooth substances, gingival recession and dentine hypersensitivity. These limitations can be partly overcome by pharmacologic therapies based on antimicrobials, probiotics and host modulation [40,42].

4) Adjunctive antiseptics

Antiseptics are used for subgingival irrigation and biofilm control. Chlorhexidine, hydrogen peroxide, sodium hypochlorite are some antiseptics used in the treatment of periodontal disease. Chlorhexidine reduces the plaque, gingivitis and it can delay subgingival bacterial recolonization. It is available in the form of mouth rinse, irrigation, spray and gel. Chlorhexidine mouth rinses can also kill bacteria present in the nondental biofilms. It provides better microbiological and clinical outcomes than scaling and root planing alone. But chlorhexidine has adverse effects such as brown staining of teeth and tongue, alterations in taste and increased calculus deposition [40,42].

5) Adjunctive systemic antibiotics

Antibiotic treatment aims to eradicate or control specific pathogens. Systemic antibiotics together with scaling and root planing will provide additional benefit over scaling and root planing alone in the treatment of periodontitis. Systemic antimicrobial therapy is provided for patients exhibiting attachment loss after conventional therapy or patients with aggressive form of periodontitis [9].

Disadvantages [43,44]

- Inadequate drug concentration at the site of periodontal pocket.
- Rapid decline of plasma drug concentration to sub therapeutic levels.
- Development of microbial resistance.
- Increased likelihood of toxic side effects.

6) Adjunctive local antibiotics

Local antibiotics are used to treat patients with localized lesions and nonresponding or recurrent sites. Local application of antibiotics causes fewer adverse effects, less risk of bacterial resistance development and better patient compliance than systemic antimicrobials. It is a better substitute for systemic antimicrobials [43,44,45].

EXAMINATION

Periodontal probing, radiographic analysis, gingival index, mobility charting, and assessment of the quantity of connected gingiva should all be included in a periodontal examination. Simple equipment and minimum clinical calibration on the part of the examiner are needed for these clinical tasks. The clinical examination includes estimating local factors, developmental discrepancies of the teeth causing increased plaque accumulation, bleeding on probing (a sign of periodontal tissue inflammation), estimating the depth of the periodontal pocket manually or using pressure sensitive probes, determining the involvement of the furcation, determining recession, and determining the clinical attachment level [46]. A set of intraoral periapical radiographs, bitewing radiographs, or a panoramic radiograph should be used to estimate bone loss after a clinical assessment [46]. Theclinical signs of advanced periodontitis, in addition to radiographic analysis, aid in diagnosis [25].

IN SITU GEL

The transitional condition between the solid and liquid phases is called a gel. The liquid phase is immobilised by the three-dimensional network of interconnected molecules that makes up the solid component [47]. After the formulation has been administered to the site, a process known as in situ gelation causes a gel to form there. In situ gel phenomenon is based on a semi-solid mucoadhesive key depot that is created from a liquid medication formulation solution [48]. In situ gel forming formulations are a revolutionary approach to provide medications to patients in a liquid dosage form while still achieving sustained drug release throughout the desired time. Different polymer-based delivery systems have been created in order to prolong the period that the formulation remains at the drug absorption site [49].

Low viscosity and exceptional adhesiveness appear to be requirements that can be met by in situ forming gel (ISG). In order to achieve the desired clinical advantages, ISG has the capacity to sustain high levels of the drug in the gingival crevicular fluid for extended periods of time. It is given as a precursor that, when applied to the areas of action, transforms into a gel. The success of in situ gels for the treatment of periodontitis depends on the phase transition from the fluid to the gel [50].

It is possible to employ different natural and synthetic polymers through oral, ophthalmic, transdermal, buccal, intraperitoneal, parenteral, injectable, rectal, and vaginal routes by in situ gel-forming them. Natural polymers utilised for in situ gelling systems include pectin, gellan gum, chitosan, alginic acid, guar gum, carbopol, xyloglucan, xantham gum, HPMC, and poloxamer [51].

It is made up of a reliable, secure, and three-dimensional component network [52]. The cross-linking of polymer chains in gels results in the creation of either covalent (chemical cross-linking) or non-covalent links as the network of polymer molecules (physical cross-linking). There are two categories of gels based on their natural makeup (i.e., physical and chemical). Weak bonds seen in physical gels include Vander Waal, electrostatic, and hydrogen bonds. Growing interest in physically crosslinked gels-chemical gels where strong covalent connections emerge—as a result of toxicity concerns [53].

MECHANISM

The various mechanisms that causes the formation of in situ gel are:

A. Physiological (e. g., temperature and pH)

B. Physical (e. g., solvent exchange or diffusion and swelling)

C. Chemical (e. g., enzymatic, chemical and photo-initiated polymerization) [54].

A. Physiological

a. Temperature activated in situ gel systems:

Systems that thermally initiate or induce in situ gelling at a certain temperature. In these systems, gelation cannot be produced by heat sources other than body heat. These systems are the most popular ones. The engineering of the thermoresponsive sol-gel polymeric system uses primary techniques. This thermally induced or thermally sensitive in situ gel technology is divided into three categories for ease of use. Moxifloxacin hydrochloride is a case study for a temperature-triggered in situ gel system that uses carbopol 934P and poloxamer 407 as polymers [55].

i. The type that is negatively thermosensitive, such as poly-N-isopropyl acrylamide (PNIPAAm)

ii. The type that is positively thermosensitive, such as polyacrylic acid (PAA), poly (acrylamide-co-butyl methacrylate), or polyacrylamide

iii. Thermally reversible type, including polymerized poloxamer, pluronic (poloxamer), tetronics (poloxamines), and others (ethylene oxide)-b-poly (ethylene)-b-poly (propylene oxide) [56].

b. pH-activated systems

In this method, a gel will be created using pH-responsive or pH-sensitive polymers. All pH-sensitive polymers have acidic or alkaline ionizable functional groups that, in response to a change in pH, either release or allow absorb protons. Poly-electrolytes are a very large class of ionizable groups.

These polyelectrolytes raise the pH outside, which causes hydrogels to swell and create in situ gels, some of the anionic groups employed as pH triggered systems. The use of mixtures of poly-methacrylic acid (PMA) and PEG as a pH-sensitive system to accomplish gelation is another example. Other examples include cellulose acetate phthalate (CAP), polyethylene glycol (PEG), pseudo latexes, polymethacrylic acid (PMC), carbomer, and its derivatives, etc. The PAA (carbopol, carbomer) or its derivatives are the most commonly found anionic pH-sensitive polymers. Doxycycline is a good example of a pH-responsive in situ gel system because it uses polymer N,N-dimethylformamide [55,57,58].

B. Physical

a.Swelling:

When a substance collects water from its surroundings and expands to fill a desired space, in situ creation gel is formed. Myverol 18-99 (glycerol mono-oleate), a polar lipid that expands in water to generate lyotropic liquid crystalline phase structures, is one such chemical. It has some bioadhesive qualities and is susceptible to enzymatic degradation in vivo [59].

b.Diffusion:

With this technique, the solvent from the polymer solution diffuses into the tissue around it, precipitating or solidifying the polymer matrix. It has been demonstrated that a suitable solvent for this system 16 is N-methyl pyrrolidone (NMP). Doxycycline hyclate utilising hexane as the solvent is an example of an in situ gel system for solvent exchange [60].

C. Chemical

a.Ionic cross linking:

Ionic cross linking: A change in the ionic strength of the instilled solution causes gelation. The gelation rate is determined by the osmotic gradient around the surface of the gel. The gelation is brought on by a change in the ionic strength of the injected solution. The osmotic gradient at the gel's surface controls how quickly it gels. The fluids in the mouth cavity contain several electrolytes, such as Ca2+, Mg2+, and Na+ cations, which are essential for the beginning of gelling when the solution is injected into body cavities. Alginates, hyaluronic acid, and gellan gum or gelrite are examples of polymers [61,62]. Metronidazole is an example of an ion-activated in situ gel system, and gellan gum is used as the polymer [55].

b.Enzymatic cross linking:

Under physiological settings, an enzymatic process functions effectively without the need for potentially dangerous substances like monomers and initiators. The use of hydrogels that can release insulin in intelligent stimuli-responsive delivery systems has been studied. In reaction to changes in blood glucose levels, cationic pH-sensitive polymers with immobilised insulin and glucose oxidase can swell, releasing the insulin that has been held in a pulsatile manner. The mixes can be injected prior to gel formation by conveniently managing the rate of gel formation by adjusting the amount of enzyme [63].

c.Photopolymerization

Photopolymerization is a technique commonly used to create biomaterials in situ. At long ultra violet (UV)-visible wavelengths, a mixture of monomer andphotoinitiator polymerizes. For photopolymerization, long UV-visible wavelengths are preferred. Short UV-visible wavelengths are generally avoided because they can cause biological harm and limit tissue penetration. Because photopolymerization occurs quickly with rapid photo-initiators, acrylates are commonly used as polymerizable groups. Camphorquinone and dimethoxy-2 phenylacetophenone act as photoinitiators for UV and visible photopolymerization, respectively [64].

Table No. 2 Polymers Used As In Situ Gelling Agents.

POLYMER	PROPERTIES	MECHANISM	EXAMPLE
Pectin	Pectins are a type of polysaccharide in which the polymer primarily consists of --(1-4)—D galacturonic acid residues [66].	Low methoxypectins readily form gels in aqueous solution in the presence of free calcium ions. Pectin gelation occurs in the presence of H+ ions. When pectin is taken orally, divalent cations in the stomach carry out the transition to gel state [66].	Theophylline[65].
Guar gum	Guar gum is water soluble but insoluble in hydrocarbons, fats, esters, alcohols, and ketones. These demonstrate its dispersibility in both cold and hot water, as well as its ability to form colloidal solution in both cold and hot water at low concentrations[67].	Temperature variations cause reversible changes in gel formation [67].	Linezolid[68].
Xyloglucan	Xyloglucan is a polysaccharide derived from tamarind seeds that has a (1-4)—D-glucan backbone chain with (1-6)—D xylose branches that are partially substituted by (1-2)—D-galactoxylose [68].	When xyloglucan is partially degraded by -galactosidase, the product exhibits thermally reversible gelation due to the lateral stacking of the rod-like chains. The temperature at which the sol-gel transition occurs varies with the degree of galactose elimination. When warmed to body temperature, it forms thermally reversible gels [68].	Pilocarpine [69].
Gellan gum	Gellan gum is an anionic deacetylatedexocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one -L-rhamnose, one -D-glucuronic acid, and two -D-glucuronic acid residues [51].	It has a gelation tendency that is temperature dependent or cation induced. This gelation involves the formation of double helical junction zones, which are then aggregated to form a three-dimensional network via complexation with cations and hydrogen bonding with water [51].	Metronidazole[55].
Alginic acid	Alginic acid is a polysaccharide composed of -D-mannuronic acid and -L-glucuronic acid residues linked by 1,4-glycosidic linkages. Depending on the algal source, the proportion of each block and the arrangement of blocks along the molecule differ [51].	Dilute aqueous solutions of alginates form firm gels upon addition of di and trivalent metal ions via a cooperative process involving consecutive glucuronic residues in the alginate chain's -L-glucuronic acid blocks [51].	Secnidazole [55].
Chitosan	Chitosan is a naturally occurring component of shrimp and crab shells that consists of a biodegradable, thermosensitive, polycationic polymer formed by alkaline deacetylation of chitin. Chitosan is a biocompatible cationic polymer with a pH of 6.2 that can remain dissolved in aqueous solutions [71].	By adding polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose, or glucose phosphate salts to chitosan aqueous solution, the pH gelling cationic polysaccharides solution is transformed into thermally sensitive pH dependent gel forming aqueous solutions without any chemical modification or cross linking[71].	Levofloxacin[55].
Carbopol	Carbopol 934 is polymerized in benzene after being cross-linked with allyl sucrose [72].	Carbopol is a pH-dependent polymer that forms a low viscosity gel at alkaline pH but remains in solution at acidic pH [72].	Curcumin[55].
Poloxamer 407	Poloxamers are a class of non-ionic difunctional triblock copolymers that are commercially available. They are made up of a central block of relatively hydrophobic polypropylene oxide that is surrounded on all sides by blocks of relatively hydrophilic polyethylene oxide[73].	They are triblock copolymers made up of poly(oxyethylene) and poly(oxypropylene) units that change solubility as the temperature of the environment changes. When these molecules are immersed in aqueous solvents, they form micellar structures above critical micellar concentration due to the PEO/PPO ratio of 2:1 [73].	Moxifloxacin Hydrochloride[55].

In Situ Gel For Periodontitis

These are liquid preparations that can be easily injected into the periodontal pocket and then hardened to form a gel with a custom geometry (after solvent replacement). Under nonphysiological conditions, the gel remains as solution and forms a gel under physiological conditions under the control of stimuli such as pH, temperature, ions, and solvent present in the oral cavity. In situ gel delivers drug at a controlled rate directly to the target site, reducing side effects and improving patient compliance. The main advantages of in-situ implants are that they can be easily injected into periodontal pockets, harden to form a solid implant with customised geometry, have time-controlled drug release, and do not require the removal of empty remnants [74].
Merits include [51,54,55]:

a. Patient compliance

It is critical to be able to administer accurate and reproducible amounts in comparison to already formed gel. The benefits of an in situ forming polymeric delivery system include improved patient compliance and comfort, as well as ease of administration and reduced administration frequency.

b. Controlled delivery of drug

Because of its unique 'Sol-Gel transition,' in situ gels promote controlled drug release after administration. Accurate dosing and controlled drug release from in situ gels result in no drug accumulation and no side effects.

c. Bioavailability

In situ gel is one of the most promising local drug delivery systems because it has the potential to keep high levels of the drug in the gingival crevicular fluid for extended periods of time, allowing for the desired clinical benefits. As a result, bioavailability is improved.

d. Ease of administration

They are easily injected into periodontal pockets, harden to form a solid implant with customised geometry, drug release that is time-controlled, and there is no need to remove the empty remnants.

e.Ease of metabolism

The use of biodegradable and water-soluble polymers in in situ gel formulations can make them more acceptable and excellent drug delivery systems, and they can finally be rapidly eliminated through normal catabolic pathways, which is a significant advantage over other delivery systems.

CONCLUSION

The injectable in situ gel formation system has tremendous potential for the treatment of periodontitis because it allows for the controlled release of drugs for site-specific management. The in situ injection gel formation system has great potential for the treatment of periodontitis because it allows the timing of drug release to be controlled based on the treatment of the specific site. The primary requirement of a successful controlled release product is improved patient compliance, which in situ gels provide. The use of polymeric in-situ gels for controlled drug release offers several advantages over traditional dosage forms. They adhere strongly to the surfaces of the teeth and provide adequate mechanical strength to ensure consistent and prolonged residence times in periodontal pockets. The in situ gel forming system with an array of polymers that have synergistic action in combating and reversing periodontal disease is likely to remain attractive.
In the coming years, the emphasis should be on in vivo profiling of these systems under in situ gel formulation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

ISG-In Situ Gel,
RANK -Receptor Activator of Nuclear Factor-kB,
CP-Chronic periodontitis,
AgP-aggressive periodontitis,
LAP-Local aggressive periodontitis,
GAP-global aggressive periodontitis,
NHANES III-National Health and Nutrition Examination Survey III,
HSV-herpes simplex virus,
CAL-Clinical Attachment Loss,
NUG-necrotizing ulcerative gingivitis,
NUP-necrotizing ulcerative periodontitis,
HPMC-Hydroxy Propyl Methyl Cellulose,
PNIPAAM-poly-N-isopropyl acrylamide,
PAA-polyacrylic acid,
poly-methacrylic acid PMA-poly-methacrylic acid,
PEG- as a pH-sensitive system to accomplish gelation is another example. Other examples include cellulose acetate phthalate (CAP), polyethylene glycol (PEG),
pseudo latexes, polymethacrylic acid (PMC),
PEG-Polyethylene glycol,poly-methacrylic acid (PMA),
cellulose acetate phthalate (CAP),
polymethacrylic acid (PMC),
NMP-N-methyl pyrrolidone.

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