



## A 4-D approach for amelioration of periodontitis<sup>☆</sup>

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### ABSTRACT

Global prevalence of the severe periodontitis is at the alarming stage and its association with the systemic complications is highly evident which cannot be neglected. An insight into the pathophysiology of the periodontitis reveals that the promising amelioration could only be envisaged with the 4-D/multi-pronged approach of combining antibiotic along with the host modulating agents. The complications of the disease itself suggest that the use of antibiotic alone is not able to cater the symptoms completely. There is a need of other host modulatory agents too, such as Cyclo-oxygenase –II (COX II) enzyme inhibitors, Matrix metalloproteinase's (MMPs) inhibitors and osteo-integrating agents. Also, there is an unmet need of singular treatment modality through which all these agents can be sequentially and directly delivered into the periodontal cavity. The current hypothesis takes it a step forward wherein an antibiotic is combined with other three host modulatory agents in a singular drug delivery system. The encapsulation of multiple therapeutic agents with controlled release would therefore allow for reduced drug dose thus minimizing side effects; contributing to enhanced patient compliance and treatment efficacy. Hence this approach can be presented as a 4-D/multi-pronged approach for circumvention of periodontitis.

### Introduction

Severe Periodontitis is the 6th most prevalent disease and globally 11.2% population is suffering from this oral infection [1]. Periodontal affliction can be defined as the infection mediated inflammation of gingiva and periodontal tissue, leading to gingivitis, pyorrhea and halitosis. It's a progressive disease wherein advanced stages results in the destruction of bone supporting tissue, alveolar bone loss and development of periodontal pocket due to collagen degeneration [2].

Pathophysiology of periodontitis suggests that it is a vicious circle of dental disease which starts with the gingivitis. The primary cause of gingivitis is the poor or ineffective hygiene which leads to deposition of the bacterial flora on the gum line also known as biofilm or dental plaque. The microbiota mainly includes anaerobes or facultative anaerobes like *Porphyromonas gingivalis*, *Prevotella intermedia*, *Bacteroides forsythus*, *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum* [3]. Bacterial plaque and its byproducts primarily lead to periodontal connective tissue destruction and alveolar bone loss. Biofilm deposition in periodontitis provokes host response in

terms of gingival inflammation which is the result of activity of cyclo-oxygenase-II enzyme (COX-II) in the gingiva [4]. If left untreated, gingivitis progresses to the periodontitis, leading to destruction of collagen (gingival fibers) by the matrix metalloproteinase enzymes (MMP) on the tooth collagen [5]. This leads to separation of gum tissue from the tooth, as a result of which, deep pockets are formed called as periodontal pockets, and ultimately alveolar bone loss occurs because of the suppression of Bone Morphogenetic Protein (BMP) [6].

### Current treatment strategies for periodontitis

In general the treatment strategy of periodontitis involves surgical procedures, conventional approaches and novel periodontal drug delivery systems and are discussed as follows-

1. Surgical Treatment- It includes mechanical debridement of periodontal pocket with plaque control measures to remove bacterial infection. Surgical treatments involve scaling and root planning, flap surgery and gingivectomy. However, it has been shown that these

**Abbreviations:** MMPs, Matrix metalloproteinase's; COX-II, Cyclo-oxygenase-II; BMP, Bone Morphogenetic Protein; NSAID'S, Non-steroidal anti-inflammatory drugs; HMT, Host Modulation Therapy

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procedures are not efficient for halting the disease and also are financially challenging [7].

2. Conventional treatment- Treatment with conventional drug delivery system involves high dose of systemic antibiotics and anti-inflammatory agents. Systemic antibiotics such as tetracyclines, clindamycin, penicillins, metronidazole and macrolides are mainly indicated in the periodontitis [8]. But high dose of these antibiotics leads to excess burden on the body leading to systemic side effects and restricting their long term usage [7].
3. Novel periodontal drug delivery systems- These types of systems involves local and controlled delivery of antimicrobials. Local delivery of antimicrobial assures site specific delivery and maintained the therapeutic level of drug at the site of infection for prolonged periods of time. Controlled delivery of therapeutic agents within periodontal pockets can alter the pathogenic flora and improve the clinical signs of periodontitis. A plethora of novel drug delivery systems are available for periodontal pocket delivery. But they may suffer from disadvantages like need of mechanical bonding of delivery system to the tooth surface, inability to reach into the deeper regions of periodontal cavity, requirement to remove the remnants of non-biodegradable delivery systems and poor patient compliance [7,9]. Apart from the systemic and localized delivery of antimicrobials, parallel research is being carried out in other fields, such as (a) the low-dose antibiotics, which act as inhibitors of collagenase [10], (b) the use of NSAIDs, which block the inflammatory pathway involved in periodontal tissue destruction [11], (c) The use of enzyme inhibitors which can inhibit alveolar bone resorption [12,13] and (d) the use of nano-composite biomaterials in the form of cement [14,15].

**Perioceutics**

The new field perioceutics (Periodontal + therapeutics) is defined as the combination of antimicrobial therapy and host modulatory therapy, to produce beneficial changes in the microflora and host response, respectively [16]. Various host modulatory agents can be summarized as Non-steroidal anti-inflammatory drugs (NSAID’s), Matrix-metalloproteinase inhibitors (MMP inhibitors), Anticytokines, Bone-morphogenetic Proteins (BMPs) and Pro-resolution factors [17]. Further, host modulation therapy (HMT) is a treatment concept that aims:

- To stop the tissue destruction and stabilize or even regenerate the periodontium by modifying or down-regulating destructive aspects of the host response, and up-regulating protective or regenerative responses
- To restore the balance between pro-inflammatory mediators and destructive enzymes on one hand, and between anti-inflammatory mediators and enzyme inhibitors on the other hand [18].

All these approaches are self sufficient to enter a challenging new phase in dental research. But ultimately, the development of effective treatments will depend upon the work that combines molecular understanding of the disease and the success of delivery systems in the complex biological environment.

**Hypothesis**

Based on the extensive literature survey done, we can state that currently there is no ideal therapeutic approach to completely treat periodontitis and to achieve predictable tissue regeneration. As the progression of periodontitis involves a complex, sequential relationship between infection, inflammation and tissue loss, there is an unmet need of a singular system through which all required host modulatory agents along with the antibiotic can be efficiently delivered. So, the aim is to design a suitable vehicular system for the delivery of multiple

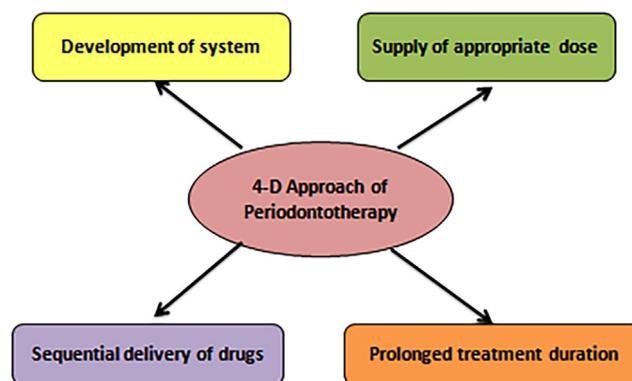


Fig. 1. 4-D approach of periodontotherapy- Can be categorized into following four aspects; 1) development of system, 2) supply of appropriate dose, 3) sequential delivery of drugs and 4) prolonged treatment duration.

therapeutic agents. Also for the complete elimination of infection, the effective concentration of the antibiotic should maintained for 10–15 days in the periodontal cavity [19], hence the vehicular system should bathe the periodontal cavity for at-least 15 days with the antibiotic. Moreover, for other host modulatory agents the dose is very crucial as in higher doses the host modulatory effect will not be produced. Thus, prolonged drug release with the appropriate dose is an important requirement.

The challenging task of the current hypothesis is to produce a vehicular system in which all the agents can be loaded in separate compartments so that they will not hamper each other’s activity and will also be released in a predetermined sequential manner.

So, the current work, as shown in Fig. 1, technically revolves around the 4-D approach for periodontitis, which includes the “development of system, delivery of drugs with appropriate dose and prolonged treatment duration”.

The hypothesized vehicular system can be explained with the help of Fig. 2, wherein the bone regenerating agent and anti-bone resorptive agents are to be incorporated inside the nanoparticle. Then these nanoparticles along with a COX-II inhibitor are to be encapsulated inside a microcapsule. Further, this microcapsule along with an antibiotic is to be suspended in the gel.

The said formulation is an attempt to achieve the sequential and sustained release of therapeutic agents and can be explained with Fig. 3.

**Evaluation of hypothesis**

By reviewing prior art and literature, it is observed that limited attempts have been made to develop long acting, sustained release and

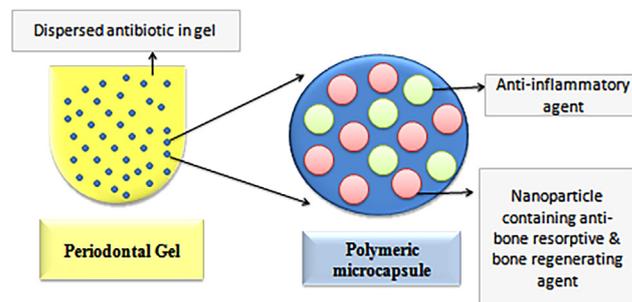
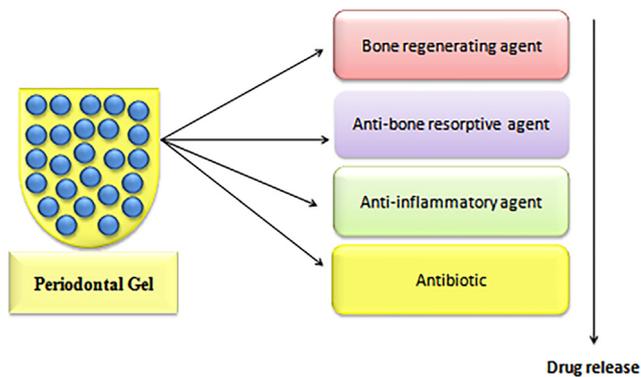


Fig. 2. Schematic representation of proposed formulation design- Periodontal gel containing dispersed antibiotic and polymeric microcapsules which are loaded with anti-inflammatory agent and nanoparticles. Further nanoparticles are loaded with bone resorptive agent and bone regenerating agent inside the shell.



**Fig. 3.** Drug release pattern from the periodontal gel—Drug release follows the sequential pattern wherein antibiotic release is followed by anti-inflammatory agent, which is further followed by anti-bone resorptive agent. And at the end, release of anti-bone resorptive agent is followed by bone-regenerating agent.

multi-drug delivery formulations for periodontitis. Hence the primary purpose of this hypothesis is to design a 4-D approach for periodontitis. Each aspect of the above mentioned approach is discussed in the following sections.

- To be able to successfully treat periodontitis, a combination of various therapeutic agents such as antibiotic, COX-II inhibitor, anti-bone resorptive and osteogenic agent is required and the rationale is as follows-
  1. Antibiotic namely minocycline is chosen to kill the infection causing bacteria that is *Porphyromonas gingivalis*. It's a bacteriostatic agent with broad spectrum of activity against both Gram positive and Gram negative organisms. Interestingly it is effective against beta-lactamase producing strains which are present deep inside the periodontal cavity and are even resistant to the penicillins [20].
  2. Celecoxib is selected as a COX-II inhibitor because evidences in the form of animal studies and human studies are there to support the fact that the prostaglandins, a metabolite of arachidonic acid plays an important role in periodontitis. If there is local tissue injury then plasma membrane phospholipids releases arachidonic acid, then it gets metabolized by the cyclooxygenase (COX-I and COX-II enzymes are involved) pathways and produces prostaglandins [21,22]. Long back NSAIDs (Non-steroidal anti-inflammatory drugs) were prescribed by the dentists to treat the periodontitis associated pain and inflammation but the systemic side effects precluded their use. Later on clinical trials suggests that COX-II enzyme is primarily responsible for the production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) during periodontal infection and COX-II inhibitors can be a better alternative to the NSAIDs. Therefore amongst the selective COX-II inhibitors, celecoxib is used in our study [23].
  3. The rationale behind selecting the doxycycline hyclate is based on the fact that the tetracyclines have the ability to suppress the host modulation through the inhibition of matrix-metalloproteinases (MMPs). MMPs are solely responsible for the destruction of tooth supporting collagen and are secreted by the macrophages, neutrophils, fibroblasts and osteoclasts cells of the periodontium. Studies have shown that amongst the three tetracyclines, doxycycline hyclate in subantimicrobial dose is more effective in suppressing the matrix-metalloproteinases [24]. Thus the ability of doxycycline hyclate as an anti-bone resorptive agent is exploited in our study.
  4. Hydroxyapatite is employed as the bone regenerating agent as the ultimate goal of the periodontotherapy is the reconstruction of the tooth supporting structures which are lost due to periodontal disease. For regeneration/reconstruction of periodontium,

appropriate positioning of the collagen, cementum and bone synthesizing cells is important. And use of bone replacement graft materials is the attractive technique to achieve the periodontal tissue regeneration. Further bone grafts can be replaced with calcium phosphate based inorganic like hydroxyapatite. Hydroxyapatite is structurally and chemically similar to the mineral component of the bone [15,25]. Literature supports that the use of hydroxyapatite based biomaterials considerably helps in improving the clinical attachment level of the tooth and the probing depth [26,27].

- However, the periodontitis is associated with multiple symptoms but literature suggests that all the conventional drug delivery systems encapsulate and deliver maximum of two therapeutic agent [28–32], but for effective treatment outcomes, multiple drugs are required. In one study, Sundararaj et al. 2013 delivered four therapeutic agents namely antibiotic, NSAID, MMP-inhibitor and BMP promoter in sequential and controlled manner with the polymeric films in the periodontal pocket [33]. Their study confirms the sustained and controlled release but insertion of periodontal films in the cavity requires the surgical procedure and this comes out to be the major drawback of this delivery system. Whereas, Baek et al. 2017 suggested a novel approach to incorporate multiple drugs in separate compartments inside a delivery system [34]. With this singular platform all aspects of our 4-D approach can be fulfilled. Hence the proposed formulation as shown in Fig. 2, will be in the form of periodontal gel, containing suspended antibiotic (minocycline) and polymeric microcapsules. Further the polymeric microcapsules contain a COX-II inhibitor (celecoxib) and nanoparticles. These nanoparticles encapsulate MMP inhibitor (doxycycline hyclate) and bone regenerating agent (hydroxyapatite). And the drug release from the gel follows the sequential pattern as shown in Fig. 3.
- Next step towards the 4-D approach is the dose optimization of all therapeutic agents. For the targeted antibiotic MIC of *P. gingivalis* is already given in the literature [35]. From the dose ranging studies, minimum effective concentration of the COX –II inhibitor is known [23,36]. Also for the MMP inhibitor USFDA has prescribed the dose [24,37]. Lastly for the bone regenerating agent, a fixed amount will be loaded in the formulation. So, initially the dose can be decided as per the literature but finally can be fixed on the basis of dose ranging studies.
- The main concern of the periodontotherapy is the prolonged drug delivery, and the major challenge is to formulate a polymeric system through which duration of drug delivery can be extended. As per Lee et al, 2001 for complete elimination of infection, it is necessary that the MIC of the antibiotic should be maintained for at-least 10–15 days in the periodontal cavity [19]. In order to achieve the sustained and prolonged drug therapy, various polymers were explored [37–40] and provides an insight that by altering the ratios of polymers, extended drug release can be obtained, that ultimately fulfills the criteria of 4-D approach and leads to the success of delivery system.

## Conclusion

Oral afflictions like periodontitis have long been ignored; nonetheless its association with severe diseases like carditis, low birth weight baby and preeclampsia has instigated dedicated research in this area. The current work is one such pursuit of developing a singular and sustained drug delivery system intended at circumventing all symptoms like bacterial infection, inflammation and bone loss. Dental treatments are often expensive and use huge doses of systemic antibiotic therapy as well as anti-inflammatory agents, whilst the purported system offers a multi-component, locally applicable, sustained release formulation for easy use and positive therapeutic outcomes. In summary, the hypothesized approach would presciently offer a reliable treatment tool

for the various stages of periodontitis and combating effectively to antibiotic resistance as well.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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