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Local Drug Delivery Systems in the Management of Periodontitis: A Scientific Review

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ABSTRACT:
A microbial disease of the tissues supporting teeth, periodontitis (PD) causes the surrounding soft and hard tissues to gradually deteriorate, eventually leading to tooth movement and exfoliation. Periodontitis is an inflammatory disease induced by complex interactions between the host immune system and pathogens that affect the integrity of teeth supporting tissues. To prevent disease progression and thus preserve the alveolar bone structure, simultaneous anti-inflammatory and osteogenic intervention is essential. Selection of a right antimicrobial agent with appropriate route of drug administration is the key to successful periodontal therapy. Irrigating systems, fibers, gels, strips, films, micro particles, nanoparticles and and low dose antimicrobial agents are some of the local drug delivery systems (LDDS) available in the field, which aims to deliver antimicrobial agents to sub-gingival diseased sites with minimal or no side-effects on other body sites. The present review aim to summarize the current state-of-the-art technology on LDDS in periodontal therapy ensuring the practitioners are able to choose LDD agents which are custom made for a specific clinical condition.

1. INTRODUCTION

1.1 Periodontal diseases: definitions and classifications

Periodontal or gum diseases are a group of inflammatory disorders that compromise the supporting tissues of teeth and share common clinical manifestations. Based on the progressive nature of periodontal diseases, they can be divided into two main stages. First, gingivitis which is an early and non-destructive inflammatory disease that occurs when dental plaque accumulates around teeth and affects soft tissues surrounding the teeth. It causes gum swelling with a tendency to bleed upon slight provocation[1].

Second, periodontitis, the focus of this dissertation, is the destructive stage of periodontal disease that is associated with bleeding upon probing, increased probing depth, and may cause gingival recession. It can present in a localized or generalized form and characterize by periodontal inflammation of soft and hard tissues leading to periodontal attachment and alveolar bone loss[2]. Periodontitis can be classified based on its progression into chronic and aggressive. The chronic form is most prevalent in adults and characterized by slow and progressive attachment and bone loss, while aggressive form results in rapid and severe attachment loss and bone destruction[3].

The disease afflicts 45.9 % of adults in the United States, confirming the high burden of periodontitis[4]. Men are more likely to have gum disease than women, and teenagers rarely develop periodontitis, but they can develop gingivitis. Furthermore, the harmful health impact of periodontitis is not only limited to the local tissue destruction and alveolar bone resorption, but it may also affect systemic health by increasing the incidence risk of systemic inflammatory diseases, atherosclerosis, and cancer[5].

Periodontitis is a multifactorial non-communicable inflammatory disease characterized by chronic progressive destruction of the tooth-supporting apparatus, affecting all parts of the periodontium, and causing irreversible damage [6]. The term periodontal disease is an umbrella term used to describe chronicinflammatory conditions of the soft tissues or

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supporting tissues surrounding the teeth [7,8].In its severe form, periodontal disease, a biofilm-induced chronic inflammatory condition of the tissuessupportingtheteeth,affectsmorethan700millionindividualsworldwide[9,10].

In the India 50% of adults have gingivitis affecting at least 3-4 teeth; two-thirds of the population has sub gingival calculus, and about a one-third have periodontitis. Periodontal treatment aims to cure inflamed tissue, reduce the number of pathogenic bacteria and eliminate the diseased pockets. Periodontal disease is known to begin with the inflammation of the gingiva. This inflammatory response is often initiated by bacteria in a biofilm surrounding the teeth and dental supportingtissues in the form of plaque [11,12]. In circumstances of uncontrolled inflammation, there is associated damage to teeth and supporting tissues, asillustratedinFigure1.

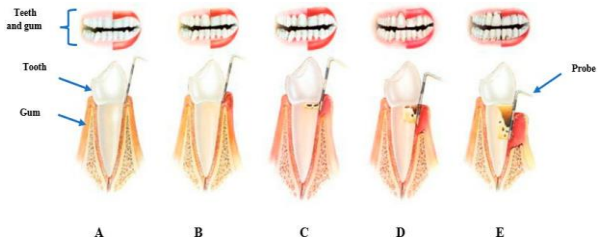

Figure 1. Schematic diagram of the progression of Periodontal disease (**A**) represents healthy teeth and gum characterized by pink gums with fresh breath and no bleeding with brushing.(**B**) Gingivitis marked by red swollen gums with bleeding during brushing, possible bad breath, no bone loss. (**C**) Early stages of periodontitis, with red swollen gums that bleeds during brushing, mild bone loss, possible tooth mobility and bad breath. (**D**) Moderate periodontitis with red swollen bleeding gums, persistent badbreath, moderate bone loss, tooth mobility and root exposure. (**E**) Severe periodontitis characterizedby red swollen gums that bleed with brushing, advanced bone loss, possible tooth loss and persistent bad breath [13].

Periodontal infections are a significant cause of tooth loss and can have negativeimpacts on overall health. It is not surprising that several studies have identified a bidirectional association between periodontal disease and other systemic conditions such as coronary heart disease [14], Cognitive disorders [15], diabetes [16], and other cardiovascular diseases [17].Owing to the debilitating effect of periodontal disease, it is known to have a significant impact on the health status and quality of life of individuals.

Nanogel can be termed as dispersion of hydrogel by physical and chemical cross-linking polymer at nanoscale size. “Nanogel” was first introduced to define cross-linked bifunctional networks a polyion and a nonionic polymer for delivery of polynucleotides and Polyethylene Glycol (PEG). They are soluble in water and allow spontaneous loading of drugs in aqueous media. Nanogel has ability to regulate size, composition depending upon the application. Nanogel can be used as additive in various applications such as paint, cosmetics, medical etc. Nanogel is employed to load drugs and followed by stimuli-sensitive, multi-responsive, magnetic and targeted drug delivery application and also in bioimaging. Comparison to other preparations nanogel shows a strong inhibition at very low quantity [18,19].

1.2 Types of periodontitis

The periodontitis can be classified into two main categories in which one is chronic periodontitis where disease progression occurs slowly to moderate rates [20]. Males and females both are susceptible, while male’s susceptibility is more than females for chronic periodontitis [21]. Heavy smokers have a high risk of occurrence of chronic periodontitis [22] due to an elevation of catalase (CAT) enzyme, glutathione peroxidase (GSH-Px), and reduction in superoxide dismutase (SOD) and glutathione levels in gingival tissues [23]. The hypo-oxygenated environment is produced by the smoke components and this favors the growth of anaerobic bacteria which leads to the destruction of tissue due to a reduction in vascular supply [24]. The second one is the aggressive periodontitis (disease progression occurs in rapid rates) occurs in younger individuals (less than 25 years of age) [20]. Depressive mood, weight loss, loss of appetite, and fatigue are strongly related to aggressive periodontitis. The clinical features of aggressive periodontitis included diastema formation with distolabel migration of the incisors, sensitivity due to exposed root, deep dull pain, and periodontal abscess with lymph node enlargement. Women are highly affected by aggressive periodontitis [21]. The periodontitis may classify on the basis of stage, extent and distribution, and grades. The classification of periodontitis is as follows [25]:

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1. Stages: based on the severity and complexity of management

Stage I: initial periodontitis

Stage II: moderate periodontitis

Stage III: severe periodontitis with the potential for additional tooth loss

Stage IV: severe periodontitis with the potential loss of dentition

2. Based on the extent and distribution

a. Localized

b. Generalized

c. Molar-incisor distribution

3. Grades: evidence or risk of rapid progression, anticipated treatment response

a. Grade A: slow rate of progression

b. Grade B: moderate rate of progression

c. Grade C: rapid rate of progression

1.3 Risk factors

1.3.1 Smoking: It has been clinically established and demonstrated that a positive correlation between cigarette smoking and a higher risk for periodontal disease and alveolar bone loss is clear[26]. Nicotine is one of the most pharmacologically active compounds in cigarette smoke. It has been shown to promote collagen breakdown and to inhibit gingival fibroblast growth and production of fibronectin and collagen in vitro, which are vital components to a healthy periodontium[27]. Furthermore, it has been shown that when periodontal cells exposed to nicotine, the growth and protein content were decreased. Also, damaged cell membranes and atypical shapes were observed[28]. Nicotine also has been evidenced to stimulate osteoclast differentiation and the resorption of calcium phosphate which may illustrate the severity of alveolar bone loss and refractory disease incidence 3 in smokers[29]. Nicotine has also been shown to delay apoptosis which would allow for osteoclasts to persist the resorptive process[30].

1.3.2 Diabetes: Both type 1 and type 2 diabetes mellitus has been confirmed as a major risk factor for periodontal diseases[31-33]. The risk of periodontitis is increased by approximately three fold in diabetics compared with non-diabetic individuals, and higher risk with poor glycemic control[34]. When glucose is elevated in saliva, harmful bacteria grow in saliva and combine with food to form a soft plaque. In a study of 350 diabetic children (6–18 years old) vs 350 non-diabetic controls, the proportion of periodontal disease was greater in the children with diabetes (>20% vs 8% of sites, respectively)[35]. The mechanisms by which diabetes affects periodontal health are complicated and still not solely defined. It has been proposed that upregulated pro-inflammatory cytokines, the formation of advanced glycation end-products (AGEs), and reactive oxygen species (ROS) are mechanisms that affect periodontal tissues. It has been reported that the level of pro-inflammatory cytokines PGE2 and IL-1β is higher in GCF of diabetics when compared to non-diabetics[36]. AGEs bind to their receptor (RAGE), which is overexpressed in diabetics[37], and stimulate pro-inflammatory cytokines[38,39] and also induce osteoblast apoptosis[40]. As oxidative stress is increased in diabetes, superoxide is increased in the mitochondria which lead to greater inflammation[37,41].

2. PATHOGENESIS

2.1 Oral microbiology and pathogenesis

More than 700 bacterial taxa have been identified to date, which inhabits different niches in the oral cavity by forming biofilms at distinct sites on a tooth (fissures, approximal surfaces, and gingival crevice) and reflects the inherent differences in their anatomy and biology. The oral bacteria have long been considered to be mostly commensal with only a small proportion being pathogenic [42]. The oral microbiome is in continuous interaction with environmental factors and its host [43]. Under homeostatic conditions, the oral microbiome is stable and in symbiosis with its host. However, environmental perturbations can lead to a shift into dysbiotic biofilms which can be a causative factor of dental caries and periodontitis [44]. Periodontal disease is essentially a mixed bacterial infection that produces inflammatory destruction of the tissues that surround and support the teeth. It occurs as a result of a combination of factors, but its primary cause is bacteria found in dental plaque. When left untreated, the disease often causes damage to the affected teeth, accounting for the majority of teeth lost during adulthood. Periodontitis can also cause complete dislocation of the tooth from the socket [45].

In general, anaerobic, gram negative, facultative micro-organisms are the main bacteria related to periodontal disease [46,43]. It is particularly impossible to prove that the involvement of specific microorganisms causes pathogenesis of periodontitis. Periodontitis bacteria colonize at the gingival crevice and combined with intra-periodontal pockets [46]. The

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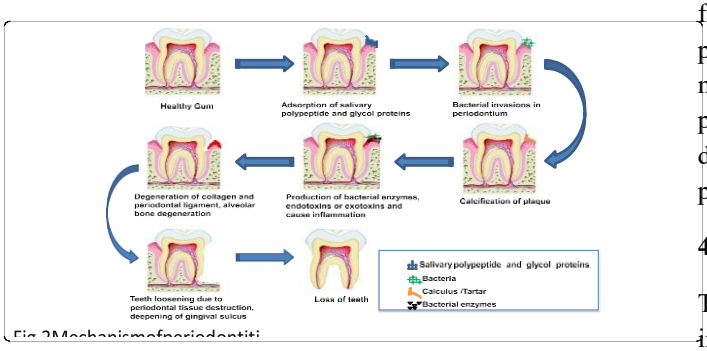
biofilm of plaque is formed at the area of non-self-cleanable. In marginal periodontitis, the biofilm originates from the gingival sulcus, and in the case of advanced periodontal disease, it arises from the gingival pocket [46].

2.2 Periodontal pocket

The formation of periodontal pockets is pathologically dependent on gingival sulcus and is the most important clinical feature of periodontitis. The continuous pocket formation leads to destruction of periodontal supportive tissue, which causes loosening or damage to teeth. Periodontal pocket forms either by microorganisms or their products and causes deepening of the gingival sulcus. The bacterial plaque initiates an inflammatory process in the tissue wall of gingival sulcus and the form pocket. The normal gingival sulcus turns into a pathological periodontal pocket and depends on the number of bacteria present in the dental plaque. The mechanism of periodontitis induced tooth loss is shown in Fig. 2. The tissues surrounding the gingival, including fibers, are degenerated due to the exudate product of bacterial cells. Collagen fibers can be lost by two mechanisms, either by local immune response or collagenase and lysosomal enzymes that become extracellular from macrophages and leukocytes at the interface of the ligament and cementum [46].



The disease initiates with gingivitis which is considered a significant risk factor for developing periodontitis, an irreversible immune reaction. It characterized by the loss of teeth-attached oft tissues and severe alveolar bone resorption which may lead to teeth loss. It has been reported that gingivitis does not always develop into periodontitis, indicating that in addition to plaque accumulation, host susceptibility is necessary to develop periodontitis(5). Once periodontitis is established, a pro-inflammatory cytokine cascade would initiate the destruction of soft and hard tissues. It is well reported that pro-inflammatory cytokines secreted by monocytes, lymphocytes, and some resident fibroblasts are responsible for the disease progression[47]. Interleukin-1β (IL-1β) is considered one of the most potent inducers of bone resorption and is reported to be elevated in inflamed gingival tissues and gingival crevicular fluid (GCF) promoting connective tissues destruction through inducing matrix metalloproteinases (MMPs)[47]. Subsequently, interleukin-6 (IL-6) is secreted in response to bone resorbing inducers including IL-1β[47]. This inflammatory cascade promotes osteoclastogenesis by disrupting the balance between receptor activator of nuclear factor kappa-B ligand (RANKL) and its decoy receptor osteoprotegerin (OPG). The RANKL will be overexpressed to interact with receptor activator of nuclear factor kappa-B (RANK) receptor expressed on the osteoclast precursor cells, promoting osteoclast activation and initiating alveolar bone resorption[48, 49].

3. DIAGNOSIS AND TREATMENTS

According to the National Health and Nutrition Examination Survey data, about 11% of the earth populations are alive with severe periodontitis. Periodontitis has wide-spreading and is related to the development of several systemic diseases. Prevention is better than cure and is beneficial to oral health for the prevention of periodontitis. Proper diagnosis and treatment becomes very important for a patient suffering from periodontitis. Periodontal inspection, probing, palpitation, and radiography (current clinical diagnostic methods) cannot meet the requirements to detect periodontitis. Therefore, there is an urgent need to develop a rapid and costeffective method for diagnosing periodontitis [50].

4. LOCAL DRUG DELIVERY SYSTEMS

The use of systemic drug administration for treating oral infection in the last 50years has shown positive results [51,52]. Nevertheless, the use of systemic administration for drugs gives many disadvantages, such as dysbiosis and low quantities of the drug in the site where it is desired. However, this may cause gastrointestinal problems, drug resistance, and toxicity [53-55].

Therefore, over the past 30 years, local drug delivery systems (LDDSs) have obtained an interest in studying how to use drugs in specific site where it is needed and how to control their release. For this purpose, polymers as drug carriers were discovered. They can defend the bioactive agents during the delivery into the body and have the quality to regulate the release kinetics. The

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bioactive principle can be filled with the polymeric matrix or linked in the polymeric chain [56]. Drug delivery systems allow to control and prolong the release of drugs into a specific site, and it can also be contained within different target agents simultaneously. In this way, reducing the dose and the number of intakes of drugs [57, 58] is possible. The use of an LDDS can give more benefits than systemic administration. It can bypass gastrointestinal problems and the systemic metabolism of the drugs before reaching the site of interest, giving LDDS a higher efficiency [57, 58]. Moreover, LDDS allows for administering in a noninvasive way the drug in the subgingival pockets [59]. Additionally, this type of drug administration allows loading two or more drugs of different categories in the same moment into the periodontal pockets [60]. Fibers, irrigations, membranes, films, nanoparticles (NPs), and microparticles are some of the forms of LDDS created [61]. The LDDS, which gives curative effects for periodontal issues, includes three main categories of drugs: antibacterial, inflammation-modulating, and alveolar and bone repairing agents.

Fibers:

The term fiber is derived from a Latin word 'Fibra' which means a natural or a synthetic substance whose length is significantly greater than its width. Fibers are reservoir type of therapeutic formulation system that are placed circumferentially into the periodontal pocket using an applicator and sealed with a cyanoacrylate adhesive or a periodontal dressing [62,63]. Electro spinning is one of the most frequently used methods of fabrication of fibers, which provide unique characteristics such as surface to volume ratio, drug loading efficiency and ease of administration.

Matrix system: strips and films

Strips and films (SF) are polymer based thin bands of matrix system designed to deliver the active therapeutic agents in a controlled and sustained fashion when precisely placed in the interproximal periodontal pocket space[68]. A Japanese periodontist Noguchi, demonstrated the application of these systems in the year 1984 [69]. Direct milling or solvent casting method are primary methods of fabrications of films using various polymers, while other techniques include hot melt extrusion, rolling solid dispersion extrusion, and semisolid casting [70].

Gels

Gels are dilute, cross-linked semisolid systems in which liquid particles/ the active drug molecules are uniformly dispersed in a solid medium that exhibits no flow when in the steady-state [77,78]. Gels get the maximum credit in the general dental practise for being used ubiquitously as a carrier system to deliver therapeutic agents in a wide range of oral diseases such as oral ulcers, denture stomatitis and desquamative gingival lesions. These wide applications are made possible owing to the properties such as ease of preparation and administration, sustained drug release pattern, minimum dose frequency and drug toxicity [79,80]. In periodontics, gels with active therapeutic agents are delivered into subgingival pocket gently by using wide port needle syringes to ensure a uniform distribution throughout the diseased site.

Microparticulate system

Microparticles are solid spherical polymeric structures with a diameter range of 1–1000 μm designed to contain active therapeutic agents, dispersed uniformly throughout the polymeric matrix, which allows protection of drugs from the external environment, elimination of incompatibility, or masking of unpleasant taste, enhance bioavailability and sustained therapeutic activity [91].

Nanoparticulate drug delivery (NP) system

In the recent years, nanoparticles (dimension less ≤100 nm) are gaining extensive attention in the biomedical field owing to their ability to accurately deliver the active therapeutic agents to the target site [100,101]. These NP are delivered to the site of action either directly or after loading with active drugs for sustained and controlled release. Silver, gold, titanium dioxide and copper NP are some of the most widely researched metallic nanoparticles in dentistry and other biomedical field due to their antimicrobial, anticancer, and bone regeneration potential [102–106]. Further, functionalized superparamagnetic NP have been investigated in diagnostics and treatment of human cancers [107]. Other NP include liposomes, polymeric NP, polymeric micelles and solid lipid NP [102]. Improved transport across cell membranes, more surface area-to-volume ratios which results in improving drug loading capability, and biocompatibility as the size of the particles simulate the structure of the biological tissues are some of the key advantages of NP [108].

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Table 1

Studies investigating role of various LDDS for the periodontal therapy.

LDDS	Polymer	Drug	Method of formulation	Inferences	Reference
Fibers	Poly (lactic acid)	Chlorhexidine (0.5%–1.0% *w*/w)	Electrospinning	Sustained release was observed for 650 h in pre-encapsulating chlorhexidine particles with polyelectrolyte multilayers. The formulation demonstrated antibacterial activity against *E. coli* and biocompatibility against human fibroblasts.	2017 [64]
	poly(L-lactide-*co*-d/L-lactide)	Ampicillin and metronidazole (20/20 m%)	Multijet electrospinning	The formulation demonstrated drug release in a concentration dependent manner with an effective antimicrobial activity against *Aa*. *Fn*, *Pg.* and *Enterococcus faecalis* and non-toxic against human gingival fibroblasts.	2016 [65]
	Sodium alginate	Ciprofloxacin (200 mg), Diclofenac sodium (500 mg)	Syringe-extrusion technique using barium chloride as crosslinking agent.	The formulation exhibited zero-order drug release with antimicrobial activity against E. *coli*, *E. faecalis* and S. *mutans* for 10 days.	2013[66]
	Poly(L-lactide-co-d/L-lactide) 3–5% (w/w)	Metronidazole (0.1–40%)	Electrospinning	The formulation exhibited sustained drug release for period of 28 days. Fibers showed effective antimicrobial activity against F. *nucleatum Pg* and *Aa* and was cyto-compatible against human gingival fibroblasts.	2012 [67]
Strips and films	2% chitosan (from crab shells), Glycerine (0.5%) as plasticizer and Glutaraldehyde solution for cross linking	Metformin hydrochloride	Casting method	The film showed sustained release of metformin over a period of 11 days. Further metformin film showed desirable antibacterial and bone regenerating potential in periodontitis induced animal	2018 [71]

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JCHR (2024) 14(1), 839-844 | ISSN:2251-6727

			model.	
sodium alginate (4%*w*/*v*), gelatin (4%w/v), diammonium hydrogen phosphate calcium hydroxide, calcium chloride as crosslinking agent	Tetracyclines	Solvent casting method	The composite film demonstrated significant stability and ease of handling. Drug release was observed for > 10 days.	2018 [72]
Gelatin (2.58–5.41% w/v)	Curcumin (2 mg)	Solvent casting technique.	Developed film efficiently released curcumin for period of 7 days with promising effect in management of periodontitis.	2018 [73]
Non-amidated low methoxy pectin	Metronidazole (5%)	Casting or modified ionotropic gelation techniques.	The developed films showed desirable mechanical and radial swelling properties. Antimicrobial activity observed against *Pg* and *Aa*. Film demonstrated preliminary burst release with subsequent slow release for 7 days.	2018 [74]

LDDS	Polymer	Drug	Method of formulation	Inferences	Reference
	Carboxy methyl cellulose sodium (CMC) or sodium alginate (ALG) 6% and Thiolated sodium alginate (2 or 4%w/v)	Metformin (0.6% *w*/w)	Double casting technique	An in-vitro and clinical study of the developed multiple layer film was carried out. Invitro study suggested that the developed film had good mechanical properties, enhanced mucoadhesion and a controlled form of drug release. The clinical results suggested an improvement in all the clinical parameters in the management of moderate periodontitits.	2017 [75]

	poly(lactic-coglycolic acid), methoxypoly (ethyleneglycol) (MePEG) and [poly(D,L-lactic acid)-*block*-methoxypoly(ethyleneglycol)] at final concentration of 10% w/v	Tetracycline and tetracycline hydrochloride (5% w/w)	Solvent casting method	Tetracycline HCl loaded film demonstrated rapid release as compared to tetracycline. The addition of MePEG/ diblock resulted in concentration dependent increase in release of the drugs.	2010 [76]
Gels	Water-soluble: Chitosan (2% (*w*/*v*) in distilled water), base chitosan (2% concentration in dilute lactic acid (1% *v*/v))	Atorvastatin (2% (*w*/*v*)) in polyethylene glycol 400 (PEG 400).	Conventional gel followed by Acetylation	The chitosan-based atorvastatin gel displayed desirable viscosity and syringe ability properties. It provided adequate bio-adhesion to hold the system at the application site. The release of the drug was found to be slower as compared to that atorvastatin gel prepared in PEG 400.	2018 [81]
	Cinnamon oil (oil phase) tween 80 and Carbitol® (surfactant- cosurfactant mixture), poloxamer 407 (23% w/v)	Quercetin (125 µg/200 µL)	Thermoreversible gel	Quercetin loaded nano-emulgel displayed complete release of quercetin over 6 h.	2018 [82]
	Low-viscosity chitosan (20 mg)	Thymol	Conventional gel with Acetylation	Thymol-chitosan hydrogels showed burst release within the first 48 h with antimicrobial activity against S. *aureus* and S. *mutans* for 72 h.	2017 [83]
	Poloxamer (Pluronic 127) (30% w/v), carbapol P 934 (1% w/v) and polyethylene glycol (PEG-400) (140 mg/mL)	Curcumin (2%w/w)	In-situ, thermoreversible gel	In-situ gel containing 2% curcumin showed desirable rheology with optimum spread ability and was effective in the treatment of experimental periodontitis in rats	2017 [84]

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	Poloxamer 407, carbopol 934	Cranberry juice	Poloxamer and Carbopol based Thermoreversible gel	Thermoreversible gel of cranberry juice displayed gelation temperature of ≤32 °C, ideally acceptable for subgingival application in periodontitis. In addition, (50% w/v) cranberry juice in gel showed similar zone of inhibition when compared with commercially available chlorhexidine gel (0.2%) against panel of micro-organisms associated with periodontal infections.	2017 [85]

LDDS	Polymer	Drug	Method of formulation	Inferences	Reference
	Bleached shellac (BS) 15–30% w/w was dissolved in *N*-methyl pyrrolidone (NMP)	Doxycycline hyclate (DH), Metronidazole (MT), Benzoyl peroxide (BP) (5% w/w each)	Solvent exchange-induced in situ forming gel	In situ gel was formulated in simulated gingival crevicular fluid loaded with DH, MT and BP showed drug release over the period of 48 h. Drug loaded-BS systems showed significant inhibition of *S. aureus*, E. *coli*, S. *mutans* and Pg.	2016 [86]
	Medium molecular weight chitosan (0.5% w/v), beta-glycerophosphate (1.8% w/v)	Minocycline (2% w/v)	Novel Chitosan based thermoreversible gel	Formulated thermoresponsive gel of MCL with chitosan/b-glycerophosphate showed drug release 92–99% and the pH of 5.6–6.2. The gelation temperature of the in situ gels was found to be 37 °C with stability over a period of 90 days.	2016 [87]
	Poloxamer 407 (19% w/v), Carbopol 934P (0.2% w/v)	Chlorhexidine hydrochloride (0.1% w/v)	Thermoreversible gel	Chlorhexidine hydrochloride, in situ temperature-sensitive gel was successfully formulated and the assessed parameters were	2013 [88]

				found to be satisfactory with sustained drug release for a period of 6 h.	
	Eudragit RS (35%w/w), *N*-methyl pyrrolidone (NMP), polyethylene glycol (PEG) 1500 (2.5–10%) and peppermint oil (5–15%)	Benzoyl peroxide (BPO) (1–20%)	Thermoreversible gels	The viscosity and syringe ability of the prepared systems was directly proportional to the amount of BPO, peppermint oil or PEG 1500. Prepared gels caused sustained BPO release for at least 96 h. All gels followed the Newtonian flow which revealed decrease in the viscosity with increase in the temperature.	2013 [89]
	Gellan gum (0.6–1.0% w/v), lutrol F127 (14–18% w/v)	Ornidazole (1% w/v)	Thermoreversible gel	Gel were found to be dependent in the polymeric concentration for optimization of gelation temperature. Likewise, drug release was decreased as increase in each polymer component. Gel formulated with 0.8% w/v of gellan gum and 16% w/v of lutrol F127 revealed optimised physical characteristics.	2010 [90]
Microparticles	Dextran sulfate (DS), $CaCl_2$	Minocycline (2 mg/mL)	Ion pairing complexation	The ion pairing/complexation of minocycline, Ca^{2+}, and sulfonate/ sulfate-bearing biopolymers, achieved sustained release for 9 days. The antimicrobial activity was effective against *Aa* and *Sm*.	2018 [92]
	Polylactic-*co*-glycolic acid	Phenytoin, Nifedipine, Cyclosporine	O/W emulsion	Phenytoin, nifedipine or cyclosporine-loaded PLGA microspheres showed control release and the clinical study conferred the therapeutic benefits toward gingival recession and alveolar bone	2018 [93]

Journal of Chemical Health Risks

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			loss.	
Chitosan, Sodium tripolyphosphate, ethyl Cellulose	Doxycycline hyclate (200 mg)	Coacervation-solvent displacement	Positively charged, bio/mucoadhesive Chitosan/sodium tripolyphosphate microparticles showed sustained release of Doxycycline hycylate and exhibited a high mucoadhesive property.	2018 [94]
Variants of polyhydroxyalkanoates (PHA)	Tetracycline (40% w/w)	Double emulsion-solvent evaporation	The tetracycline loaded PHA microspheres in micro and nanoscale showed slow release behavior. The release rate of drug was influenced by the PHA and showed efficient killing activity against periodontitis-causing bacteria.	2016 [95]

LDDS	Polymer	Drug		Method of formulation	Inferences	Reference
	Poly (L-lactide-co-glycolide)	Doxycycline (w/w)	20%	Double emulsion solvent evaporation	Locally-delivered Doxycycline loaded Poly L-lactide-*co*-glycolide microspheres in the periodontal pocket of patients with chronic periodontitis showed sustained release after administration.	2015 [96]
	Chitosan solution (1% (w/v))	Clindamycin phosphate (0.25–4% w/w)		Spray-drying method	Biodegradable spray-dried chitosan microparticles loaded with clindamycin phosphate with encapsulation efficiency of > 80%. It	2014 [97]

				showed initial burst release due to the water solubility of the drug, but the increased amount of chitosan decreased the drug release rates.	
	Chitosan solution (1%w/w), Tween20/ Tween80, Span80, Glutaraldehyde	Metronidazole (20 mg)	Emulsion cross-linking process	Metronidazole-loaded chitosan microparticles produced using 1% of Span80 in soybean oil, 5% glutaraldehyde based on chitosan solution with 1:1 drug: chitosan ratio, showed prolonged release property.	2013 [98]
	PLGA and zien from maize	Tetracycline (0.125%)	Spray drying method	Suitable drug release profile in the range of 5–7 days was obtained from different hydrogels containing metronidazole loaded microparticles. The release was mainly dependent, on the concentration of zien.	2012 [99]
Nanoparticles	Silver nitrate (AgNO3) (5 mM) in collagen	Silver nanoparticles suspensions in collagen	Simple reduction method	Synthesized nanoparticles demonstrated dose dependent antibacterial activity against periodontal pathogens and were found to be biocompatible against human gingival fibroblasts	2018 [109]
	PLGA copolymers and Chitosan (1% w/w)	Metronidazole or N-phenacylthiazolium bromide	Oil- in- water emulsion solvent evaporation	Formulation demonstrated initial rapid drug release at pH 5.5 whereas the drug was completely released in 7 days. It	2018 [110]

Journal of Chemical Health Risks

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				reduced subgingival inflammation in experimental periodontitis in rats.	
	Chitosan chloride, Sodium alginate and pectin	Crosslinker	Ionotropic gelation	Effect of pure and Nano formulations of chitosan, alginates and pectin nanoparticles is demonstrated. Alginate nanoparticles remained stable at salivary environment. However, it was found to be cytotoxic at in-vitro experiments. And, chitosan nanoparticles were found to be Cyto-compatible.	2017 [111]
	Sodium alginate: ZnCl2	Cetylpyridiniumchloride (CPC)	Ionotropic gelation	Particles with diameters < 200 nm, polydispersity index < 0.2, negative zeta potential and spherical morphology were formulated. The entrapment efficiency was 94% with loading capacity > 50% and prolonged release over 7 days. The formulations with noted charge ratios resulted in stable CP-alginate nanoparticles with a potential of treating periodontal disease.	2016 [112]

LDDS	Polymer	Drug	Method of formulation	Inferences	Reference

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 839-844 | ISSN:2251-6727

Poly-ε-caprolactone, Pluronic F-68	Eugenol	Solvent displacement method	Eugenol-loaded Nano capsules (NCs) was found to follow a biphasic pattern and followed Michaelis–Menten like model. In-vitro cell viability assay indicated that the NCs are not cytotoxic and in vivo performance of the eugenol-loaded NCs using ligature-induced periodontitis model in rats indicated that eugenol-loaded NCs could prevent septal bone resorption in periodontitis.	2016 [113]
2-hydroxyethyl, methacrylate, (HEMA), *O*-carboxymethyl chitosan (O-CMC) $CaCl_2$	Beads of Calcium sulfate incorporated with Tetracycline nanoparticles	Ionic gelation method	Tetracycline nanoparticles with entrapment efficiency of 89% showed a cumulative release of 27% at the end of 10 days following a sustained release pattern. The antibacterial activity and cytocompatible nature of developed nanoparticles could be beneficial in periodontal management to reduce the bacterial load at the infection site.	2014 [114]
Poly -e-caprolactone (50-70 mg) Pluronic F-68 (0.2-1%)	Triclosan (5-10 mg)	Solvent displacement method	Optimised triclosan loaded Poly-caprolactone NPs with particle size of 180-230 nm showed 91% entrapment efficiency and *in-vitro* release of 97% for 3h. NPs were stable with the shelf life of 17 months and demonstrated cyto-compatibility against L929 cell lines.	2013 [115]

Journal of Chemical Health Risks

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JCHR (2024) 14(1), 839-844 | ISSN:2251-6727

	PLGA	Minocycline	Single and double emulsion Solvent evaporation emulsion, ion pairing, and nanoprecipitation)	Novel minocycline-PEGylated PLGA nanoparticles prepared by the ion pairing method had the best drug loading and entrapment efficiency compared with other nanoparticles. They also showed higher in vitro antibacterial activity than the free drug.	2012 [116]
	Different grades of chitosan, ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, thioglycolic acid, bis-acrylamide (cross-linking agent) and methacrylic acid	Metronidazole benzoate	Emulsion solvent evaporation Technique	The retention time of MET at its absorption site was found to be increased by formulating it into nanoparticles using thiolated chitosan (TCS)–poly (methacrylic acid) (PMAA). The nanoparticles of MET prepared from TCS–PMAA may represent a useful approach for targeting its release at its site of absorption, sustaining its release and improving its oral availability	2011 [117]
Liposomes	Lipoid S75 for liposomes, glycerol for glycerosomes and propylene glycol for penetration enhancer containing vesicles	*Citrus limon* (L.) extract (80 mg)	Thin film hydration method	Freeze-dried extract loaded liposomes, glycerosomes, and penetration-enhancer-containing vesicles prepared with propylene glycol prevented oxidative damage and inhibited bacterial proliferation.	2018 [118]
	HSPC and cholesterol (molar ratio, 2:1)	Minocycline hydrochloride (5 mg/mL)	Extrusion method	Minocycline hydrochloride loaded nanoliposomes inhibit the proliferation of murine macrophages and achieve the anti-inflammatory effects by suppressing the TNF-α	2012 [119]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 839-844 | ISSN:2251-6727

			mRNA expression witha reduced dose.	
POPC, PGDO, Cholesterol polyethylene glycol FeCl2, FeCI3	Magnetite nanoparticle	Thin film hydration method	Magnetic PEG-ylated liposomes (average size 286 nm) on exposure to external magnetic field demonstrated deeper penetration in to the dentinal tubules compared to PEG-ylated liposomes (average size 204.3 nm).	2012 [120]

5. CONCLUSION

Researchers and clinicians are becoming more and more interested in finding a novel treatment plan to combat the tissue destruction brought on by the complex interaction between the pathogenic microorganisms and the host defense mechanisms as our understanding of the etio-pathogenesis of periodontitis advances.

It is important to note that because pathogens invade tissue, mechanically debridement of the diseased soft and hard tissue surfaces and the root surface may not be enough to stop additional tissue loss and promote the regeneration of the lost tissue. In order to attain the greatest clinical outcomes, it is crucial for the clinician to think about using pharmacological drugs as an adjuvant to traditional periodontal therapy using the proper delivery systems.

Not surprisingly, many such plants are those traditionally used by indigenous communities to treat infectious diseases. The evidence is accumulating that the use of plant extracts enhances the antibacterial activity of conventional antibiotics, serving to repurpose these compounds rather than replacing them. There are numerous other advantages associated with the use of synergistic therapies. The plant-derived component would require a facile screening process to ensure that it is non-toxic, thus reducing the cost of development and testing while enhancing its speed to the market.

Periodontal disease is one of the most important concern for dentists and patients. It is recognized as a major public health problem throughout the world and is the most common cause of tooth loss in India. The periodontium is that the specialized tissues that both surround and support the teeth, maintaining them within the maxillary and mandibular bones. A variety of triggering factors like bacterial causes, dyscrasias, avitaminosis etc., cause inflamed gums leading to gingivitis. In the India 50% of adults have gingivitis affecting a minimum of 3-4 teeth; two-thirds of the population has sub gingival calculus, and a few one-third have periodontitis. Periodontal treatment aims to cure inflamed tissue, reduce the number of pathogenic bacteria and eliminate the diseased pockets. This study was concluded to develop dental nanogel containing clove oil and tannic acid as the chief constituent for the treatment of dental problems by novel approaches.

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