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Review Article

Local Drug Delivery Systems: A Literature Review

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Abstract

In order to complement non-surgical therapy in periodontitis, there are multiple options of antimicrobials, such as metronidazole, chlorhexidine, minocycline, doxycycline, and tetracycline etc which can be locally delivered into the mucosa. These medications are applied within periodontal pockets to hinder or eradicate periodontal disease-causing microorganisms, while also regulating the inflammatory reaction of tissues. This review seeks to assess the impact and effectiveness of various forms of localized drug delivery systems on clinical parameters within periodontology. The supplemental utilization of localized drug delivery systems featuring controlled release characteristics may offer a specific yet constrained advantageous effect on periodontal pockets. Moreover, employing local drug delivery for either active treatment or maintenance therapy hinges on clinical observations, treatment responses detailed in literature, intended clinical results, and the dental and medical backgrounds of patients, encompassing their prior antimicrobial usage.

Keywords: Periodontitis; Doxycycline; Tetracycline; Metronidazole; Minocycline; Chlorhexidine; Local Drug Delivery

Introduction

Chronic periodontitis manifests as an infectious condition leading to inflammation in the supporting structures of teeth, gradual loss of attachment, and bone deterioration, marked by the formation of pockets and/or gingival recession. It stands as the most prevalent type of periodontitis, with detection most commonly in adults, though it can begin at any age. The prevalence and intensity of the ailment rise with advancing age. It can impact a varying number of teeth and exhibits varying rates of advancement [1].

Historically, conventional treatments for periodontal disease have involved mechanical cleaning to disrupt sub-gingival bacteria and achieve smooth, biologically compatible root surfaces. To augment this approach, the incorporation of antimicrobials, administered both systemically and locally, could bolster treatment protocols. Systemic antimicrobial agents have the potential to eliminate bacteria unresponsive to scaling and root planing. Nevertheless, challenges such as drug toxicity, bacterial resistance development, drug interactions, and patient adherence constrain the use of systemic antimicrobials. To address these limitations, researchers have extensively explored localized delivery methods of antibacterial agents into periodontal pockets [2].

The supplementary application of LDD could offer significant benefits, particularly in targeted areas where traditional therapies may fall short. These systems are particularly suitable for patients undergoing maintenance treatment, those with medical limitations preventing surgical intervention, individuals in institutional care, areas of localized treatment resistance, and cases of implant failure. Additionally, their use before regenerative surgery aims to enhance predictability by minimizing bacterial presence [3].

Various agents used in local drug delivery system

- Tetracycline
- Doxycycline
- Minocycline
- Metronidazole
- Chlorhexidine

Other drugs like clarithromycin, Alendronates, ofloxacin, clindamycin, etc

Tetracycline

Tetracyclines are antibiotics with broad-spectrum bacteriostatic properties effective against a range of bacteria, including both Gram-positive and Gram-negative types, as well as Rickettsia, Mycoplasma, Chlamydia, and Spirochaeta species. They do not act in viral or fungal infections. The chemical structure of this antibiotic group is anchored in the 4-membered tetracycline ring, influencing various physicochemical characteristics including alkalinity, limited water solubility, and stability. In 1979, Dr. Max Goodson and colleagues pioneered the development of tetracycline in hollow fiber form [4].

Tetracycline based products

- **PERIOCOL-TC:** The PerioCol-TC vial contains around 25 mg of fish type I collagen infused with approximately 2.0 mg of tetracycline hydrochloride. This mixture is sterilized using gamma radiation. PerioCol-TC releases tetracycline *in vitro* for 8 to 10 days. PerioCol-TC is stored in a dry place between 5° C (41° F) and 25° C (77° F) and has a shelf life of 2 years with proper storage [5].

- **ACTISITE (TETRACYCLINE FIBERS):** The Actisite tetracycline fibers have received approval from both the United States Food and Drug Administration (FDA) and regulatory agencies within the European Union for treating adult periodontitis. These fibers are non-resorbable cylindrical devices designed for drug delivery. They consist of a biologically inert plastic copolymer infused with 25% tetracycline HCl powder. It is 0.5 mm in diameter and 23 cm in length. This is a controlled delivery device that is able to maintain concentrations of tetracycline in gingival fluid in excess of 1,300 µg/ml for a 7-day period with mean concentrations of 43 µg/ml in the superficial portions of the soft tissue pocket wall [5].
- **PERIODONTAL PLUS AB:** Periodontal Plus AB is a bio-resorbable tetracycline fiber composed of 25 mg of pure fibrillar collagen uniformly saturated with approximately 2 mg of tetracycline hydrochloride. The fibers are arranged in a strip comprising four separate sterile product packs, each individually packaged and detachable.Top of Form The fiber biodegrades in the periodontal pocket within 7 days [6]. Khan FY., *et al*. (2014) evaluated and compare the efficacy of resorbable collagen-based tetracycline fibers (Periodontal Plus AB fibers) given as an adjunct to scaling and root planing, with the clinical effects of scaling and root planning delivered as a monotherapy, in the treatment of chronic periodontitis and concluded that the delivery of antimicrobial agent tetracycline in a collagen matrix was found to improve the benefits of scaling and root planing by a larger magnitude in patients with moderate-to-deep pockets [7].
- **TETRACYCLINE GEL:** The Periodontal Gel Formulation containing tetracycline-serratiopeptidase has demonstrated statistically significant outcomes when used in conjunction with scaling and root planning. Injectable Poly (ortho ester) formulations, which are bioerodible and designed for controlled delivery of tetracycline, demonstrated complete *in vitro* degradation concurrent with drug release, with options loaded with either 10% or 20% tetracycline [8]. Top of Form

Doxycycline

Doxycycline, functioning as a bacteriostatic agent, possesses the capability to down-regulate MMPs, a group of zinc-dependent enzymes responsible for breaking down various extracellular matrix molecules such as collagens. Doxycycline gel serves as a controlled-release delivery product for sub-gingival application. It demonstrates a wide spectrum of activity against common periodontal pathogens such as *Aggregatibacter actinomycetemcomitans (Actinobacillus actinomycetemcomitans), Prevotella intermedia, Porphyromonas gingivalis, Fusobacterium nucleatum, Eikenella corrodens* and spirochetes It is a biodegradable formulation containing

- 10% by weight doxycycline
- 33% by weight poly (DL-Lactide)
- 57% by weight N- methyl 2-pyrrolidone

Doxycycline-based products

Atridox

The only FDA-approved 10% doxycycline gel system, known as Atridox (containing 42.5 mg of doxycycline), is a sub-gingival controlled-release product comprised of a two-syringe mixing system. Syringe A contains the delivery vehicle, which is a bio-absorbable, flowable polymeric formulation consisting of poly (DL-lactide) dissolved in N methyl-2-pyrrolidone, while syringe B contains 50 mg of doxycycline hyclate. When combined, the resulting product contains 10% w/w doxycycline hyclate. The constituted product contains 10% w/w doxycycline hyclate [9].

Ligosan slow release

Ligosan Slow Release is a resorbable doxycycline gel for periodontal application, containing 14% (w/w) of the active ingredient. It comes packaged in a laminate pouch and requires refrigerated storage.Top of Form It comprises single-application cylinder

cartridges, available in quantities of 1, 2, 4, 8, 10, or 16, with each cartridge containing 260 mg of Ligosan Slow Release. To use the product, insert the cartridge into the caulking gun, activate the spray nozzle, and then dispense the gel into the base of the pocket [10]. Gurkan A., *et al*. (2008) evaluated the post-treatment effects of sub-antimicrobial dose doxycycline on clinical parameters and gingival crevicular fluid transforming growth factor-β1 in severe, generalized chronic periodontitis on thirty-five patients with severe, generalized periodontitis results ensure further data for beneficial effects of adjunctive SDD therapy in the management of severe chronic periodontitis [11].

Minocycline

Minocycline belongs to the tetracycline class of antibiotics and has a broad spectrum of activity. Its bacteriostatic, antimicrobial activity results from the inhibition of protein biosynthesis. It has been tried clinically via in three different modes

Film, Microspheres, Ointment

- **Film:** Ethyl cellulose films, incorporating 30% Minocycline, were examined as sustained release mechanisms. Findings from the study suggested that employing this device could potentially achieve total elimination of pathogenic flora from the pocket within a 14-day period [12].

- **Microsphere (Arestin):** Recently, the FDA approved Arestin, a novel locally administered sustained release formulation of minocycline microspheres, designed for sub-gingival application. Encapsulated within bioresorbable microspheres (20-60μm in diameter) in a gel carrier, the 2% minocycline boasts a resorption time of 21 days. Upon contact with gingival crevicular fluid, the polymer undergoes hydrolysis, gradually releasing minocycline for a period exceeding 14 days before complete resorption occurs [13].

- **Ointment:** Minocycline ointment serves as a bio-absorbable sustained delivery system, containing 2% minocycline hydrochloride within a matrix comprised of hydroxyethyl-cellulose, aminoalkyl-methacrylate, triacetine, and glycerine. Dentomycin, a gel formulation containing 2% Minocycline, has obtained regulatory clearance for treating periodontitis within the European Union. The same product is available in Japan with the name Periocline. The concentration of minocycline in the periodontal pocket is about 1300μg/ml, 1 hr after single topical application of 0.05 ml ointment (1mg of minocycline) and is reduced to 90μg/ml after 7 hrs.

Chlorhexidine

Chlorhexidine (CHX) is an antibacterial agent employed in various applications. It is a cationic polybiguanide (bisbiguanide) predominantly utilized in the form of its salts, including dihydrochloride, diacetate, and digluconate. Chlorhexidine is recognized as one of the essential medications by the World Health Organization, listed among the most crucial drugs required for a fundamental healthcare system [14]. Chlorhexidine has a wide spectrum of activity encompassing gram-positive and gram negative bacteria, yeasts, dermatophytes and some lipophilic viruses. Plaque inhibition by chlorhexidine was first investigated in 1969 (Schroeder 1969), but the definitive study was performed by Loe and Schiott (1970) [15].

Chlorhexidine-based products

- **PERIOCol-CG:** PerioCol-CG is a petite chip, weighing 10 mg and measuring 4 × 5 × 0.25–0.32 mm. It is structured as a collagen matrix, within which chlorhexidine gluconate (2.5 mg) is infused from a 20% chlorhexidine solution, constituting its active component. Top of FormThe chip is intended for placement into the periodontal pocket and undergoes resorption over a 30-day period, with its coronal edge degrading within 10 days. It releases chlorhexidine in vitro at an initial rate of around 40% to 45% within the first 24 hours, followed by a consistent linear release over 7 to 8 days. Additionally, it has a shelf life of 2 years [16].

- **PERIOCHIP:** Periochip, developed by Perio Products, offers controlled sub-gingival delivery of chlorhexidine and stands as the sole commercially available product of its kind. It was developed by Perio Products Ltd, Jerusalem, Israel and it is the only available commercial product It consists of a film measuring 5 mm x 4 mm x 0.3 mm, containing 2.5 mg of chlorhexidine gluconate. This active ingredient is integrated within a biodegradable matrix composed of hydrolyzed gelatin cross-linked with glutaraldehyde. Each chip is individually packaged in foil containers. The chip should be stored within the temperature range of 20° to 25° C (68° to 77° F), with occasional excursions allowed to 15° to 30° C (59° to 86° F). When applying the chlorhexidine chip, it is removed from the foil container using forceps and placed directly into the pocket [17].

- **CHLO-SITE:** Chlo-Site is a xanthan gel containing 1.5% chlorhexidine within a three-dimensional mesh of saccharide polymer. Each gel injection comprises 0.5 mL and is admin-

istered directly into the periodontal pocket. The gel product undergoes sterilization via gamma radiation at 2.5 Mrad and is individually packaged for delivery in pre-filled syringes of 0.25 mL capacity, equipped with a blunt side-exit needle.Top of Form Chlo-Site offers a novel, straightforward, and effective method for addressing periodontal pockets. This gel, containing 1.5% chlorhexidine, ensures comprehensive disinfection coverage at the application site for a duration of up to two weeks, providing both active and passive disinfection [18].

Metronidazole

Metronidazole (MTZ) is a synthetic compound derived from nitroimidazole, which disrupts bacterial DNA synthesis, leading to cell death (Miani 2010). It serves as an effective antimicrobial agent in periodontal disease management due to its targeted action against gram-negative anaerobic bacteria, considered a primary causative factor for periodontitis [19]. It is an effective against anaerobic bacteria and protozoa, and is prescribed in support of conventional periodontal therapy in systemic or local administration (Noyan 1997; Haffajee 2003) [20].

Future perspectives

Eliminating microorganisms from the periodontal pocket is essential in treating periodontitis. To effectively treat periodontal diseases, it's crucial to deliver anti-infective agents to the infection sites at levels that are effective for a suitable duration, while minimizing or avoiding side effects. In the realm of local drug delivery systems, innovative therapeutic agents are being developed to maximize efficacy and minimize drawbacks.

Local delivery of growth factors

Platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and pyridinoline cross-linked carboxyterminal telopeptide of Type I collagen (ICTP) are mediators crucial for mitogenesis, angiogenesis, and bone turnover, playing a vital role in the wound regeneration of periodontal tissues. Fibroblast growth factor has been successfully incorporated into local drug delivery methods. To regenerate periodontal tissues, a sandwich membrane composed of a collagen sponge scaffold and gelatin microspheres containing basic fibroblast growth factor (bFGF) in a controlled-release system was developed [21].

- **Microparticulate system:** Microparticles are solid spherical structures made of polymers, ranging in size from 1 to 1000 µm. They are engineered to encapsulate active therapeutic agents evenly within the polymer matrix. This design serves multiple purposes, including shielding drugs from external factors, mitigating compatibility issues, and concealing unpleasant tastes. Moreover, it facilitates improved drug absorption, prolongs therapeutic effects, and ensures sustained activity over time. Microencapsulation employs a variety of polymers, including biodegradable synthetic ones such as polyesters and polyanhydrides, as well as natural options like chitosan, hyaluronic acid, and alginic acid. Water-soluble polymers such as gelatin and starch, along with insoluble polymers like ethyl cellulose and polyethylene, are also utilized in microencapsulation.
- **Nanoparticulate system:** Recently, there has been significant attention in the biomedical field towards nanoparticles (NPs) with dimensions equal to or less than 100 nm, due to their capacity for precise delivery of active therapeutic agents to specific target sites. Nanoparticles are transported to the target site either directly or following the loading of active drugs, allowing for sustained and controlled release. Silver, gold, titanium dioxide, and copper nanoparticles are among the most extensively studied metallic nanoparticles in dentistry and other biomedical fields because of their potential for antimicrobial activity, anticancer properties, and promotion of bone regeneration.

Novel chitosan pva-based local delivery system

Chitosan is a natural polysaccharide that has become established as a material with great potential for use in biomedical applications. In addition, the recent success of many polymeric depot delivery systems has encouraged further research to identify new materials and develop new systems for use in regional therapy. Several strategies have been developed for preparation of stable chitosan-based depot systems for drug delivery. Chitosan can be physically or chemically cross-linked to prepare microspheres, films and gels. Chitosan has also been blended with a wide range of polymers to produce mostly two-phase systems, which have unique properties that are required for specific applications. These stable chitosan-based depot systems have been investigated for treatment of various diseases including cancer and bacterial infection.

Recent intracanal local drug delivery system

Both nanoparticulate and microparticulate systems can serve as local drug delivery agents within the root canal, typically containing antibiotics to eradicate bacterial infections and non-steroidal anti-inflammatory drugs to alleviate or eliminate post-operative pain, following mechanical cleaning, known as post-bio-mechanical preparation (BMP). Various systems of different configurations, including sharp cones, long pins, or screws, have been suggested for insertion into the root canal as temporary dressings to facilitate local drug delivery and promote healing [22].

Drugs for osseous defects

Statins

Statins such as SMV, lovastatin, and pravastatin function as specific competitive inhibitors of 3-hydroxy-2-methyl-glutaryl coenzyme A (HMG-CoA) reductase. They are extensively utilized for reducing cholesterol levels and represent a crucial and efficient strategy in managing hyperlipidemia and arteriosclerosis. Statins also appear to influence bone formation by enhancing the expression of bone morphogenetic protein-2, inflammation, and angiogenesis. This opens up new possibilities in the realm of periodontal therapy [23].

Simvastatin (SMV)

SMV, functioning as a competitive inhibitor of the enzyme HMG-CoA reductase, stands as a commonly prescribed medication for lowering cholesterol levels. Its observed pleiotropic effects have sparked optimism, particularly in the realm of bone metabolism, suggesting its potential utility in addressing periodontal defects. As a monotherapy, local drug delivery systems incorporating a variety of drugs can improve periodontal health. The antioxidant and anti-inflammatory characteristics of SMV may additionally promote the recovery process of periodontal intrabony defects [23]. Pardeep (2010) showed a greater decrease in gingival index and probing depth and a clinical attachment level gain with significant defect fill at sites treated with scaling and root planing plus locally delivered SMV gel in patients with chronic periodontitis [24].

BISPHOSPHONATE (BPs)

Bisphosphonates (BPs) are synthetic compounds resembling pyrophosphate with carbon substitutions, which attach to the mineral portion of bone and disrupt the function of osteoclasts.Top of Form They are utilized in post-menopausal women to prevent and treat osteoporosis, as well as in conditions such as Paget's disease and malignancy-induced hypercalcemia. Top of FormSystemic administration of BPs has demonstrated potential in mitigating bone loss, while their local application as an adjunct to scaling and root-planing (SRP) has been associated with reduced bone loss and improved mineral density. Nevertheless, within various types of BPs, the local application of high doses of alendronate into periodontal pockets may induce the release of IL-1 and IL-6, consequently heightening the host's inflammatory response [25].

Alendronate

Alendronate, a recent bisphosphonate, exhibits strong inhibition of bone resorption. Its overall impact could be attributed to its ability to suppress osteoclast activity, influencing bone maturation and remodeling processes, consequently prompting bone formation.

Yet, for effectiveness, it necessitates high dosage administration to sustain the required drug concentration at the osseous defect, while systemic use of BPs may lead to various adverse effects, including gastrointestinal issues, renal failure, and severe hypocalcemia. When bisphosphonates are administered systemically, they often cause gastrointestinal disturbances. However, local drug delivery circumvents most of these issues by confining the drug to the intended site, thus enabling a significantly higher local concentration compared to what is achievable through systemic administration [26]. It was supported by Avani Ar P (2012) evaluated the efficacy of 1% ALN gel as a local drug delivery system in adjunct to scaling and root planing (SRP) for the treatment of Class II furcation defectsand concluded that ALN can provide a new direction in management of furcation defects [27].

Polysaccharide-based drug delivery systems for the treatment of periodontitis

The polymeric matrix should possess an ideal blend of binding characteristics suitable for substances that interact with or are used within the human body, making biopolymers such as proteins and polysaccharides excellent choices. Even though the mechanisms underlying the functionality of these release systems remain incompletely understood and their technologies are not yet fully refined, the outcomes of certain clinical trials highlight the particular efficacy of certain natural macromolecular compounds, and to a lesser extent synthetic polymers, in enhancing the delivery and immobilization of biologically active substances [28]. Top of Form

Chitosan-based gels

Chitosan (CS) fulfills all of the aforementioned constraints for polymers usable as drug carriers, to which its strong muco-adhesive character and its intrinsic antimicrobial activity is added. CS-based gels, starting from solutions of different concentrations, can include and release tetracycline hydrochloride and metronidazole benzoate. The optimal concentration of the CS solution is 3%, which allows the modulation of the dose of the drug substance in an optimal way for the local therapy of periodontitis [29].

Gels based on miscellaneous polysaccharide

Microbial polysaccharides (gellan) or cellulosic derivatives have high solubility in water, the ability to form gels at higher concentrations, bioadhesive properties, and are being used especially in mixtures with other polysaccharides or synthetic polymers. Doxycycline and metronidazole have been newly integrated into a gel composed of hydroxyethylcellulose (HEC), poly (vinylpyrrolidone) (PVP), and calcium polycarbophil.Top of Form Antimicrobial ef-

fectiveness was assessed against A. actinomycetemcomitans, S. sanguinis, P. micra, and E. corrodens, revealing an inhibitory effect within the initial 24 hours that persisted consistently until the 13th day. Polysaccharides in this category, particularly when combined with poloxamer, can produce thermosensitive gels capable of steadily and continuously releasing the incorporated drug. Top of FormWhen poloxamer and methylcellulose are combined, they form a thermosensitive gel at ambient temperature, facilitating the controlled release of simvastatin for a duration of 10 days [30].

Hydrogel

Hydrogels are a variant of gels, characterized by a three-dimensional structure formed when hydrophilic polymer chains are interconnected through cross-linking.Top of Form Hydrogels are networks capable of absorbing significant quantities of water while maintaining their structure, unlike gels which can break down and liquefy when diluted. Due to their capacity to accommodate both water and dissolved substances, hydrogels frequently exhibit physicochemical characteristics similar to those of the natural extracellular matrix [31].

Films

The films represent matrix systems akin to nanofibers and strips, where the drug is evenly distributed within their structure, and its release is primarily accomplished through diffusion, although erosion or matrix dissolution may also contribute. Top of FormFilms composed of chitosan and loaded with cyclohexidine have demonstrated effectiveness against Porphyromonas gingivalis, exhibiting even greater efficacy compared to cyclohexidine in its free form.Top of Form Using the same polymer, biodegradable films are produced capable of encapsulating metronidazole and levofloxacin, guaranteeing a gradual and consistent release over an extended period. By merging chitosan's antimicrobial properties with its capability to accommodate antibacterial drugs, films were developed using this polysaccharide alone or in conjunction with HPMC, MC, HEC, or PVA. These films were loaded with a cetylpyridinium active ingredient, known for its bactericidal effects against certain Gram-positive bacteria like Streptococcus mutans, and even displays activity against some Gram-negative bacteria at elevated concentrations.

Fibers

Electrospun fibers, derived from a range of polymeric materials, may consist of biopolymers, synthetics, or a blend of both, offering diverse practical applications. They can function as drug delivery systems (DDS) or carriers of cells for tissue engineering. Coaxial electrospinning was employed to fabricate electrospun fibers comprising PLGA, gum tragacanth (GT), and tetracycline hydrochloride (TCH) as a hydrophilic model drug. Studies on drug release demonstrated that both the proportion of GT and the core-shell structure can effectively regulate the release rate of TCH for up to 75 days, with only 19% released rapidly within the initial 2 hours. To address the current limitations in periodontitis treatment, a tinidazole (TNZ)-loaded CS/PCL mucoadhesive hybrid nanofiber membrane (TNZPCHNF) was developed. The antibacterial effectiveness of this membrane (at TNZ concentrations of 0%, 10%, 20%, and 30%, w/w) was evaluated against S. aureus (MTCC1303). It was observed that the inhibition zone expanded, as anticipated, with the rise in drug concentration.

Conclusion

Several drug delivery and targeting systems are presently in development to achieve enhanced dissolution rates, increased saturation solubility, improved bioadhesion, and flexibility in surface modification. These advancements aim to enable more efficient and effective administration of desired and novel drugs through optimized delivery systems. Further randomized, controlled trials are necessary to clarify the types of lesions, periodontal diseases, or particular circumstances in which local delivery systems would offer the greatest benefits.Top of Form

It can be inferred that the supplemental utilization of local drug delivery could offer a specific yet restricted beneficial outcome. Top of FormNevertheless, the extent of expected change resulting from combined therapy should be understood within the context of the severity of the defects being addressed. Hence, the clinician will have to make decisions guided by the intended goals of the therapy.

Conflict of Interest

There are no conflicts of interest.

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