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Review Article

A Narrative Review on Professionally Administered Local Antimicrobial Therapy in the Management of Periodontitis

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ABSTRACT

This narrative review focuses on the most recent scientific findings regarding the clinical application of professionally administered local antimicrobial agents (LAs) in periodontal therapy. It examines the currently available drug delivery systems and provides an updated overview of their advantages, drawbacks, and clinical performance in managing periodontal disease. A literature search identified randomized controlled trials (RCTs) comparing the effectiveness of adjunctive LA therapy with conventional mechanical debridement alone. The evidence gathered indicates that integrating local antimicrobial agents with scaling and root debridement (SRD) yields notable improvements in treatment outcomes while minimizing the adverse effects commonly associated with systemic antibiotic administration. Local drug delivery (LDD) thus emerges as a reliable and targeted approach for drug administration in periodontal care. The review advocates for the use of local antimicrobials particularly in cases of localized periodontitis or in specific sites unresponsive to standard mechanical therapy. Overall, this review consolidates current insights into LDD for periodontal management, aiming to assist general practitioners in selecting the most suitable local antimicrobial agents for clinical practice.

Keywords: Scaling and root debridement, Local antibiotics, Local antimicrobials, Topical oral antibiotic, Local drug delivery, Periodontal treatment

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Introduction

Periodontitis is a prevalent inflammatory condition of the oral cavity that affects the supporting structures of the teeth. It primarily arises from the accumulation of complex polymicrobial dental plaque. The disease process is initiated by Gram-negative, biofilm-forming bacteria on tooth surfaces, which trigger a host immune response that progressively damages the periodontal tissues. This results in irreversible bone and soft tissue loss, leading to periodontal pocket formation, gingival recession, tooth mobility, and ultimately tooth loss [1]. In addition to microbial factors, genetic predisposition has been increasingly recognized as a contributing risk factor in periodontitis. Moreover, interactions between genetic and environmental factors are thought to play a critical etiological role, though current understanding of these mechanisms remains incomplete. The pro-inflammatory cytokine interleukin-1 (IL-1) has been identified as a central mediator of host immune responses to bacterial infection and a major regulator of extracellular matrix degradation and bone resorption, processes that underlie severe forms of adult periodontitis [2].

Management of periodontal disease typically involves: (1) mechanical debridement through scaling and root debridement (SRD); (2) the use of antimicrobial or antiseptic agents to disrupt or inhibit microbial metabolism; and (3) modifying the ecological environment of pathogenic microorganisms at the tooth–periodontium interface [1]. Among these,

mechanical debridement remains the cornerstone of periodontal therapy and has proven effective for most patients. However, when used alone, it presents a higher risk of disease recurrence, particularly in individuals with systemic health conditions [1, 3–5]. Furthermore, achieving complete plaque and calculus removal in anatomically complex or inaccessible areas—such as deep periodontal pockets (>5 mm) and furcation sites—can be challenging, often resulting in incomplete debridement and limited clinical success [6].

Given these limitations, antibiotics—both systemic and locally administered—have long been used as adjuncts to SRD in periodontal treatment [3]. However, frequent or prolonged use of systemic antibiotics can result in adverse effects such as bacterial resistance, secondary infections, and issues with patient compliance [7]. Since periodontitis is a localized infection, targeted local therapy is generally preferred to minimize systemic side effects. The success of periodontal treatment largely depends on selecting an appropriate antimicrobial agent and delivery route. Local drug delivery (LDD) offers several advantages, including reduced systemic exposure, minimal side effects, and improved patient adherence compared with systemic therapy [1, 3, 7]. Studies have shown that LDD achieves significantly higher drug concentrations within the periodontal pockets compared to systemic administration [1, 8, 9].

Currently, a wide range of local antimicrobial agents—such as tetracycline (TET), doxycycline (DOX), minocycline (MIN), metronidazole (MTZ), chlorhexidine (CHX), clarithromycin (CLM), azithromycin (AZM), moxifloxacin (MXF), clindamycin (CLI), and satranidazole (SZ)—are used in diverse formulations, including irrigations, fibers, films, injectables, gels, strips, compacts, vesicular liposomes, microparticles, and nanoparticle systems [4, 7–9]. This review therefore focuses on recent evidence concerning professionally applied local antimicrobial agents (LAs) and discusses various delivery systems utilized in the management of periodontal disease.

Various local drug delivery (LDD) systems in periodontal therapy

Irrigation devices/systems

Oral irrigation (OI) involves the use of mechanical irrigation systems that may be professionally applied in clinical settings or self-administered by patients at home as a preventive measure against periodontal disease [10]. These systems function by delivering continuous water pressure to flush out bacterial deposits and their by-products from periodontal pockets through compressive hydraulic force [10]. Clinical studies have evaluated several irrigants, including 0.6% triclosan, 1% polyhexamethylene guanidine phosphate, 10% povidone-iodine, 0.25% sodium hypochlorite, 0.75% boric acid, and ozonated water at 20 mg/mL concentrations [11–19].

Results from these investigations demonstrated significant improvements in clinical parameters such as plaque index (PI), bleeding index (BI), probing pocket depth (PPD), and clinical attachment level (CAL) when these agents were used as adjuncts to scaling and root planing (SRP) compared with control groups [11–19]. Nonetheless, the therapeutic effects of irrigation systems tend to be short-lived due to their transient action, with no substantial long-term benefits observed in clinical outcomes [10–19]. These limitations have prompted the development of more advanced and sustained drug delivery systems, including fibers, films, strips, microspheres, and nanoparticle-based formulations [10].

Fibres

Fibre-based delivery systems function as reservoir-type formulations that are positioned circumferentially within the periodontal pocket using a specialized applicator and secured with either cyanoacrylate adhesive or a periodontal dressing. This configuration allows for the sustained release of antimicrobial agents directly into the periodontal site [13, 20–22]. Tetracycline (TET), a semi-synthetic broad-spectrum antibiotic with bacteriostatic properties, is commonly used in such systems. It acts by inhibiting bacterial protein synthesis and suppressing tissue collagenase activity, thereby limiting periodontal tissue breakdown [23].

Over the past decade, multiple studies have explored the incorporation of TET into fibre systems and have consistently demonstrated favorable clinical outcomes, including notable gains in clinical attachment level (CAL) and reductions in probing pocket depth (PPD) in periodontitis management **(Table 1)**. The U.S. Food and Drug Administration (FDA) approved TET fibres for the treatment of adult periodontitis in 1994 [10, 20–22]. These fibres were composed of a non-resorbable, biologically inert copolymer made from ethylene and vinyl acetate, providing controlled drug release. However, the system was later discontinued due to its non-biodegradable nature [13, 20–22].

A newer alternative, Periodontal Plus AB—a tetracycline-impregnated collagen fibre—offers the benefit of biodegradability, requiring only a single application and degrading naturally within approximately seven days in the periodontal pocket. Clinical investigations have demonstrated that this formulation leads to significant improvements in CAL

and PPD reduction compared with control groups [23–26]. Furthermore, comparative analyses between TET fibres and a xanthan-based chlorhexidine (CHX) gel (Chlosite®) revealed that TET fibres produced superior clinical outcomes, achieving greater attachment level gains and deeper pocket reduction [27].

Table 1. Summary of studies conducted over the past decade evaluating the effectiveness of locally delivered fibre-based drug systems in periodontal therapy.

Drug Delivery System	Author, Year, and Reference	Drug Used	Trade Name (if specified)	Study Design	Sample Size	Study Duration (Days)	Key Findings
Fibres	Meharwade *et al.*, 2014 [24]	Tetracycline (TET)-impregnated collagen fibres	*Periodontal Plus AB*	Split-mouth design	90 sites from 30 participants	45	Application of *Periodontal Plus AB* fibres led to significant improvements in clinical attachment level (CAL) and reductions in probing pocket depth (PPD). Gingival crevicular fluid (GCF) leptin levels dropped notably by day 15 but nearly returned to baseline by day 45. The study concluded that non-surgical periodontal therapies alone could not sustain leptin reduction, despite observable clinical gains.
Fibres	F.Y. Khan *et al.*, 2015 [25]	Resorbable collagen-based tetracycline fibres	*Periodontal Plus AB*	In vivo study	40	90	Over a 3-month evaluation period, sites treated with tetracycline fibres exhibited superior clinical outcomes compared with controls, demonstrating enhanced periodontal healing.
Fibres	Sachdeva S. *et al.*, 2011 [23]	Biodegradable tetracycline fibres	*Periodontal Plus AB*™	Split-mouth design	35	90	Combining antimicrobial therapy using *Periodontal Plus AB*™ with scaling and root debridement (SRD) resulted in more favorable outcomes than SRD alone, showing improved attachment and reduced pocket depth.
Fibres	Gill J.S. *et al.*, 2011 [27]	Tetracycline fibres and xanthan-based chlorhexidine (CHX) gel	*Periodontal Plus AB*® and *Chlosite*®	Randomized split-mouth study	30	90	The tetracycline fibre group achieved significantly greater CAL gains and PPD reduction compared with the CHX gel group, indicating higher efficacy in managing chronic periodontitis.
Fibres	Shivojot Chhina *et al.*, 2015 [26]	Tetracycline fibres	*Periodontal Plus AB*®	Randomized controlled trial (RCT)	30	90	The adjunctive use of tetracycline fibres with SRD led to improved clinical and biochemical parameters, including a marked reduction in GCF alpha-2-macroglobulin levels, confirming enhanced therapeutic response.

Matrix delivery systems—films, strips, and chips

Films, strips, and chips represent matrix-based local drug delivery systems in which antimicrobial agents are uniformly embedded within a polymeric matrix. The release of the active compound occurs through mechanisms such as diffusion, matrix dissolution, or erosion, enabling sustained and controlled drug delivery at the target site [20-22].

One of the most widely used systems, PerioChip, is a subgingival controlled-release device that delivers 2.5 mg of chlorhexidine (CHX) gluconate—equivalent to 34% CHX—within a biodegradable matrix composed of hydrolyzed, cross-linked gelatin stabilized with glutaraldehyde [10, 20-22, 28, 29]. Its key advantage lies in its biodegradability, which eliminates the need for removal after placement. In vitro analyses have

demonstrated that PerioChip exhibits a biphasic release profile—approximately 40% of the drug is released during the first 24 hours, followed by a gradual and nearly linear release of the remaining amount over a period of 7–10 days [7].

Another similar formulation, PerioCol™-CG, is a biodegradable CHX chip that contains roughly 2.5 mg of CHX gluconate embedded in a Type I collagen matrix derived from fish protein sources [20–22].

Over the past decade, several studies have assessed the clinical and microbiological outcomes associated with the adjunctive use of locally delivered, controlled-release antimicrobial systems such as films, strips, and chips **(Table 2)** [29–35]. Most findings consistently indicated that incorporating PerioChip or PerioCol™-CG as adjuncts to scaling and root debridement (SRD) resulted in significant reductions in probing pocket depth (PPD) and improvements in clinical attachment level (CAL) compared with SRD alone [29–34].

In a comparative study, Lecic J. *et al*. examined the clinical effects of different CHX gluconate formulations—CHX solution, CHX gel, and CHX chip—used subgingivally alongside SRD. The study found that all CHX preparations enhanced clinical outcomes relative to mechanical therapy alone [35]. The most pronounced improvements in plaque index (PI) were observed in the CHX solution and CHX gel groups at the one-month follow-up, while the CHX chip group demonstrated notable reductions in bleeding index (BI) and PPD at the three-month evaluation.

Table 2. Ten-year comprehensive summary of studies evaluating locally delivered, controlled-release antimicrobial matrix systems for periodontal therapy.

Drug Delivery System	Author, Year, and Reference	Drug Used	Trade Name (if specified)	Study Design	Sample Size	Study Duration (Days)	Key Findings
CHX Chip	Konuganti K. *et al.*, 2016 [29]	Flurbiprofen (FBP) and Chlorhexidine (CHX) chips	Not specified	Randomized Controlled Trial (RCT)	50	180	Subgingival administration of either FBP or CHX chips as adjuncts to scaling and root debridement (SRD) produced superior outcomes compared with SRD alone. Repeated applications of these chips yielded more significant improvements than single use.
CHX Chip	Gonzales J.R. *et al.*, 2011 [30]	CHX chip containing 2.5 mg CHX gluconate	*PerioChip*, Dexcel Pharma	RCT	24	180	Application of CHX chips before and after SRD enhanced clinical attachment level (CAL) and significantly reduced the subgingival presence of red complex bacteria.
CHX Chip	Pattnaik S. *et al.*, 2015 [31]	CHX gluconate chip	*PerioCol™-CG* (Eucare Pharmaceuticals Pvt. Ltd., Chennai, India)	Clinico-microbiological study	20	90	*PerioCol™-CG* demonstrated greater reductions in probing pocket depth (PPD) and gains in CAL, along with effective elimination of key periodontal pathogens, compared with SRD alone.
CHX Chip	Kumar A.J. *et al.*, 2016 [32]	CHX chip	*PerioCol™-CG* (Eucare Pharmaceuticals Pvt. Ltd., Thiruvakkam, Chennai, India)	RCT	30	90	Adjunctive use of CHX chips showed better clinical improvements in periodontal parameters than SRD alone.
CHX Chip	Grover V. *et al.*, 2011 [33]	CHX chip containing 2.5 mg CHX gluconate	*PerioCol™-CG* (Eucare Pharmaceuticals Pvt. Ltd., Chennai, India)	Clinical and radiographic study	40	90	Incorporating *PerioCol™-CG* with SRD enhanced both clinical and radiographic outcomes, confirming its effectiveness as a supportive therapy.

CHX Chip	Lecic J. *et al.*, 2016 [35]	CHX chip	*PerioChip*® (Perio Products, Jerusalem, Israel)	Randomized controlled, split-mouth study	15	90	The adjunctive use of CHX chips with SRD resulted in significantly improved periodontal healing compared with SRD alone, demonstrating superior clinical outcomes.

Gels

In periodontal therapy, gels serve as an effective local drug delivery (LDD) system, where the active pharmaceutical ingredient (API) is introduced into the subgingival pocket through wide-port syringe needles to ensure uniform distribution of the medication [10]. These gels are typically composed of various polymeric bases such as carbopol, xanthan gum, carboxymethyl cellulose, or chitosan, which aid in controlled and sustained drug release. Numerous gel-based antimicrobial formulations have been developed, including Chlosite, DOX, MIN 0.5%, CLM 0.5%, AZM, MXF gel, MTZ gel, 3% SZ gel, and 1% CLI hydrochloride gel, each prepared with varying drug concentrations [10, 36–53].

Chlosite, manufactured by Ghimas Company (S.p.A., Bologna, Italy), is a xanthan-based LDD gel containing 1.5% chlorhexidine (CHX) [10]. Once applied into the periodontal pocket, it gradually dissolves over a period of 10 to 30 days, maintaining a therapeutic level of CHX for at least two weeks. Its mucoadhesive nature allows it to resist dislodgement caused by gingival crevicular fluid or saliva flow.

Table 3 presents a comprehensive overview of different gel formulations used for managing periodontitis. Several randomized controlled clinical studies have investigated the effectiveness of subgingival administration of xanthan-based Chlosite® gel as an adjunctive therapy to scaling and root debridement (SRD) in patients with chronic periodontitis, diabetic individuals with periodontitis, and smokers [36–39]. Across these investigations, Chlosite® gel, when used alongside SRD, consistently produced more favorable clinical outcomes compared to SRD alone.

Table 3. Detailed study summary of investigated gel forms across the globe in the treatment of chronic periodontitis in the past 10 years

Drug Delivery System	Author, Year, and Ref. No.	Active Compound	Trade Name (if reported)	Study Design	Sample Size	Study Duration (days)	Key Findings
Xanthan-based Chlosite® gel	Jain M. *et al.* [36] (2013)	Xanthan-based CHX gel	Chlosite® gel	Randomized Controlled Trial (RCT)	30	180	Use of Chlosite® gel significantly enhanced clinical outcomes compared to scaling and root planing (SRP) alone.
Xanthan-CHX formulation	Matesanz P. *et al.* [37] (2013)	CHX in xanthan vehicle	Chlosite®, Casalecchio di Reno, Bologna, Italy	RCT	24	180	Adjunctive xanthan-CHX therapy provided slight clinical improvements; residual or recurring pockets remained, and no statistically significant differences were observed between groups.
Xanthan-based 1.5% CHX gel	Faramarzi M. *et al.* [38] (2017)	1.5% CHX in xanthan gel	CHLO-SITE®, Ghimas, Italy	RCT in diabetic patients	68	180	CHX gel may enhance the effectiveness of nonsurgical periodontal treatment in diabetic patients with periodontitis.

1.5% CHX in 0.5 mL xanthan gel	Chandra C. and Chandra S. [39] (2010)	1.5% CHX	Chlosite	Case series	74 sites from 3 chronic smoker patients	90	Combination of SRP and Chlosite® provided additional clinical benefits compared with control.
Xanthan gel with CHX digluconate 0.5% and CHX dihydrochloride 1%	Calderini A. *et al*. [44] (2013)	CHX formulations	Chlo Site (Ghimas SpA, Bologna, Italy); Corsodyl gel (GlaxoSmithKline SpA, Milano, Italy)	Preliminary case series	10	42	CHX gel offered some extra clinical advantages over SRP; CHX gluconate showed short-term benefits.
Xanthan-based CHX gel vs herbal extract gel	Phogat M. *et al*. [45] (2014)	CHX vs herbal extracts	Chlosite gel (GHIMAS, Italy)	RCT	150 sites from 30 patients	90	Herbal gel demonstrated comparable effectiveness to CHX gel in chronic periodontitis management.
Hydrophobic gingiva-adhering gel vs 1% CHX water-soluble gel	Rusu D. *et al*. [46] (2017)	Complex hydrophobic gel vs 1% CHX	Chlorhexamed 1% gel (GlaxoSmithKline, Bretford, UK)	RCT	98	180	Both gels showed similar clinical, microbiological, and enzymatic results at 3 and 6 months post-SRP.

Doxycycline (DOX) is a bacteriostatic antibiotic with broad-spectrum activity against major periodontal pathogens [40]. Following local administration, DOX concentrations in periodontal pockets reached 1500–2000 µg/mL within 2 hours and remained above 1000 µg/mL at 18 hours before gradually declining [10]. Multiple studies have demonstrated that local delivery of 10% DOX hyclate (Atridox®) effectively reduces probing pocket depth (PPD) and promotes clinical attachment level (CAL) gains [41–43].

Minocycline (MIN) gel is commonly formulated as 2% MIN hydrochloride within a matrix containing hydroxyethyl cellulose (20 mg), magnesium chloride (25 mg), eudragit (10 mg), triacetine (60 mg), and glycerine (0.5 g). A randomized controlled trial (RCT) assessing its long-term use as an adjunct to scaling and root planing (SRP) reported no significant additional benefit over SRP alone, prompting calls for further clinical trials to better establish its role [47].

Clindamycin (CLM), a traditional macrolide, possesses broad-spectrum antimicrobial activity, good bioavailability, favorable tissue penetration, and a lower incidence of side effects [48]. Macrolides can reach higher concentrations in infected tissues compared to healthy tissues [48-50]. CLM accumulates within phagocytes, monocytes, fibroblasts, polymorphonuclear cells, macrophages, and lymphocytes, which are prevalent at periodontal disease sites, suggesting enhanced therapeutic benefits [49]. Three RCTs confirmed that adjunctive subgingival delivery of 0.5% CLM in a controlled-release system improved clinical outcomes compared to SRP alone [45–47].

Azithromycin (AZM) is a semi-synthetic, acid-stable macrolide (azalide) with proven efficacy against periodontal pathogens and reduced potential for bacterial resistance in subgingival biofilms [3, 51, 52]. Although an AZM gel is not yet commercially available, three RCTs investigated the effects of 0.5% subgingival AZM gel as an adjunct to SRP in chronic periodontitis [3, 51, 52]. Specifically, Agarwal E. *et al*. studied patients with type 2 diabetes, while AR Pradeep *et al*. focused on smokers [3, 51]. Across these trials, SRP combined with 0.5% AZM gel significantly improved plaque index (PI), gingival index (GI), modified sulcus bleeding index (mSBI), PPD, and CAL compared to SRP alone [3, 51, 52].

Moxifloxacin (MXF), a fourth-generation fluoroquinolone, exerts bactericidal activity by selectively inhibiting ATP-dependent topoisomerase IV and topoisomerase II (DNA gyrase) [53]. In a study, patients with periodontitis received a single subgingival application of MXF gel at concentrations of 0.125%, 0.4%, or 1.25% immediately following full-mouth SRP. The 0.4% MXF gel demonstrated superior PPD reduction relative to SRP alone [53].

Metronidazole (MTZ) is a widely used antibiotic in periodontal therapy [7]. Elyzol® is a 25% oil-based viscous MTZ gel that has been employed in periodontitis management. Miani PK *et al*. reported that a 15% MTZ experimental gel significantly reduced bacterial counts compared to controls [54].

Satranidazole (SZ), a 5-nitroimidazole antibiotic, has also been evaluated in periodontitis treatment. Two RCTs showed that adjunctive therapy with SRP plus 3% SZ gel led to significant improvements in patients with periodontitis and type 2 diabetes compared to SRP alone [55, 56].

Microparticulate systems

Microparticles or microspheres (MC) are solid, spherical polymeric carriers ranging from 1–1000 µm in diameter, encapsulating active drugs within a polymer matrix. This design protects the drug from external conditions, masks unpleasant taste, improves bioavailability, and maintains sustained release at the target site [10, 28]. Typically, biodegradable poly-alpha-hydroxy acids such as poly(lactic acid) (PLA) or poly(lactide-co-glycolide) (PLGA) are used to encapsulate the drug, allowing gradual dissolution and local delivery of optimal concentrations [10]. Drugs such as DOX, MIN, tetracycline (TET), and CLM have been incorporated into microparticulate systems for chronic periodontitis treatment. In particular, TET and MIN are often delivered via microcapsules made from lactic acid/glycolic acid copolymers [28]. Locally delivered, controlled-release antimicrobials using microparticulate systems have consistently demonstrated clinical efficacy, as summarized in **Table 4**.

Table 4. Studies demonstrating use of microparticulate systems in the management of periodontal disease in the past 10 years

Drug Delivery System	Study (Author, Year, Ref. No.)	Drug Administered	Trade Name (if reported)	Study Design	Sample Size	Study Duration (days)	Key Findings
DOX MC	Moura L.A. *et al.* [57] (2015)	Locally applied DOX via PLGA MC	Not reported	Pilot study	19 periodontal pockets	20	By day 20, GCF drug levels dropped significantly (19.69 ± 4.70 µg/mL), and the DOX system showed effective outcomes in chronic periodontitis patients.
DOX MC	Rao S.K. *et al.* [58] (2012)	DOX MC	Not reported	Parallel, single-blind, randomized, prospective	14	180	DOX MC produced notable clinical improvements and reduced *P. gingivalis* counts in periodontal pockets.
DOX SLM	Gad H.A. *et al.* [59] (2017)	SLMs encapsulating DOX hydrochloride and MTZ	Not applicable (formulated in study pharmacy)	Split-mouth in vitro and in vivo study	12	14	SLMs were safe and showed significant enhancement in clinical and microbiological outcomes compared to SRD alone.

MIN MC	Bland P.S. *et al.* [60] (2010)	MIN hydrochloride MC	Not reported	Multicenter, single-blind, randomized, parallel-group, phase IV	127	30	MIN MC treatment substantially decreased red complex bacterial load and probing pocket depth.
MIN MC	Chiappe V.B. *et al.* [61] (2015)	MIN microgranules	Not reported	Randomized clinical and microbiological trial	26	90	Combining MIN MC with SRD improved BOP and PD, promoted CAL gain, suppressed red complex bacteria, and delayed recolonization of *Treponema denticola* versus SRD alone.
MIN MC	Srirangarajan S. *et al.* [62] (2011)	MIN MC and commercial MIN gel	Atridox (Atrix Laboratories)	Randomized, split-mouth, single-masked	50	270	MC formulation provided sustained release with higher local drug concentration and significantly improved PI and GI scores.
MIN MC + aPDT	Tabenski L. *et al.* [63] (2017)	aPDT and local MIN MC	Helbo® Photodynamic Systems; Arestin (OraPharma)	Randomized controlled trial	45	36	Neither therapy demonstrated additional significant benefits in periodontal management.

Moura L.A. *et al*. evaluated the sustained-release delivery of locally applied DOX in PLGA microparticles (MC) within periodontal pockets and reported encouraging outcomes, noting a significant reduction in gingival crevicular fluid (GCF) drug levels (19.69 ± 4.70 µg/mL) on day 20 [57]. This indicated that the drug maintained a substantially high concentration in the periodontal pocket for three weeks, demonstrating strong therapeutic efficacy. Additional studies confirmed that locally delivered DOX MC, whether administered alone or via solid lipid microparticles (SLMs) encapsulating DOX hydrochloride and metronidazole (MTZ), was effective in periodontal therapy and significantly decreased Porphyromonas gingivalis levels [58, 59].

Minocycline (MIN) is available in a locally administered, sustained-release MC form, known commercially as Arestin, with particle sizes ranging from 20 to 60 µm [10]. Multiple studies have demonstrated that adjunctive use of MIN MC with scaling and root debridement (SRD) resulted in greater reductions in bleeding on probing (BOP) and probing pocket depth (PPD), improved clinical attachment level (CAL) gains, and decreased numbers and proportions of red complex bacteria [60–62]. In contrast, a 12-month prospective randomized controlled trial by Tabenski L. *et al*. reported no additional clinical advantage of either antimicrobial photodynamic therapy (aPDT) or local MIN MC application following SRD [63]. The authors suggested that the lack of observed benefit could be attributed to high dropout rates and challenges in patient recruitment during the study period.

Tetracycline has also been formulated into microparticulate systems, where drug release kinetics are influenced by the polymer composition (lactide/glycolide ratio), molecular weight, crystallinity, and medium pH, with higher pH accelerating tetracycline release [10]. Clindamycin (CLI)-loaded microparticles have likewise been investigated, showing promising potential for periodontal therapy [64].

Nanoparticulate drug delivery systems

Nanoparticles, including nanospheres and nanocapsules, are solid-state carriers measuring approximately 10–200 nm and can be amorphous or crystalline [10]. They are designed to adsorb or encapsulate drugs, thereby shielding them from chemical and enzymatic degradation [10]. To develop an optimal delivery system for periodontal treatment, triclosan-loaded polymeric nanoparticles (PLGA, poly-lactic-acid, and cellulose acetate phthalate) were produced using an emulsification–diffusion technique [10, 28]. Madi M. *et al*. compared the anti-inflammatory effects of subgingivally delivered nanostructured DOX gel (nDOX) with conventional DOX gel as an adjunct to SRD, reporting superior improvements in both clinical outcomes and inflammatory markers over a three-month period [65].

Liposome systems

Liposome-based carriers, designed to mimic biological membranes in structure and function, have gained attention in periodontal therapy [66]. These lipid vesicles, either unilamellar or multilamellar, are composed of cholesterol, biocompatible surfactants, sphingolipids, glycolipids, long-chain fatty acids, and membrane proteins [64, 66]. They are biodegradable, non-toxic, non-immunogenic, highly stable, and protect encapsulated drugs from environmental degradation [66, 67]. However, they are expensive to produce, have limited half-lives, and may experience drug leakage or vesicle fusion [68]. Liposome systems have proven particularly effective in deep periodontal pockets in patients with severe disease [69]. A recent study by Liu *et al*. in a rat periodontitis model found that liposome gel containing 2% minocycline hydrochloride significantly reduced gingival index (GI), PPD, mononuclear cell counts, and odontoclast activity at 2, 4, and 8 weeks, while promoting new bone and fiber formation in the affected areas [70].

Other systems

A recent investigation examined the clinical, microbiological, and biochemical effects of an azithromycin (AZM) buccal patch in patients with chronic generalized periodontitis. The findings indicated that AZM monotherapy did not provide additional clinical benefits compared to conventional SRD [71].

General considerations for various local drug delivery systems (LDDs)

Clinicians must understand several factors that influence the effectiveness of local drug delivery within periodontal pockets [72]. Firstly, the antimicrobial agent should possess suitable physical characteristics to reach the targeted site and maintain an adequate concentration for a prolonged period. Ideally, the drug should exhibit zero-order release kinetics to ensure sustained presence at the site. However, the concentration of the drug can be significantly affected by the constant flow and clearance of gingival crevicular fluid (GCF). Secondly, the method of drug administration plays a critical role in therapeutic efficacy. Controlled-release devices can enhance drug performance, whereas subgingival irrigation typically produces high drug concentrations only briefly, necessitating repeated applications to achieve desired outcomes [72]. Additionally, the presence of biofilm in the periodontal pocket can hinder drug diffusion into the soft tissue, requiring disruption before drug administration. Finally, for optimal local effect, the drug concentration must exceed the minimal inhibitory concentration (MIC) [72].

Various antimicrobial agents have been employed in irrigation systems, and their success largely depends on the depth of penetration, bacterial virulence, complexity of infection, GCF flow, and sustained drug concentration within the pocket. Supragingival irrigation achieves penetration of approximately 29–71% in shallow pockets and 44–68% in moderately to severely deep pockets, whereas subgingival irrigation demonstrates superior penetration in deeper pockets, ranging from 75–93%. When used as an adjunct to scaling and root debridement (SRD), these irrigation systems produced better short-term clinical outcomes than controls, but they did not yield significant long-term improvements [11–19].

Fibre-based LDD systems, while used in periodontal therapy, have notable limitations [10]. Placement of fibres in the pocket can be time-consuming (around 10 minutes) and requires considerable clinical skill. Fibres may also cause patient discomfort and local erythema, potentially interfering with periodontal healing [10].

Matrix-based systems, by contrast, offer several advantages [10, 20–22]. The size and shape of films or chips can be tailored to the dimensions of the periodontal pocket, and insertion is minimally uncomfortable for the patient. Due to their adhesive properties and thin profile (less than 400 μm), these devices remain securely in the pocket without disrupting oral hygiene practices [10, 20–22].

Gels provide additional benefits compared to other formulations. They are easier to prepare and administer, possess high biocompatibility and bioadhesive properties, allow sustained drug release, require less frequent dosing, and minimize drug toxicity [10]. Studies summarized in **Table 3** indicate that subgingival injection of xanthan-based Chlosite® gel, when used alongside SRD, resulted in significant clinical improvements over SRD alone [36–39]. However, Calderini A. *et al*. reported that CHX gel did not provide additional benefits compared to SRD alone [44], while Phogat M. *et al*. found that xanthan-based CHX gel (Chlosite®) and herbal extract gels produced statistically similar outcomes [45]. Similarly, Rusu D. *et al*. observed comparable clinical, microbiological, and enzymatic results between CHX-based gingiva-adhering gel containing herbal components and 1% CHX water-soluble gel at 3 and 6 months post-SRD [46].

Doxycycline (DOX) may be particularly effective in conditions characterized by excessive collagen degradation, demonstrating the greatest reduction in collagenase activity compared to minocycline (MIN)

and tetracycline (TET) [40]. Atridox, an FDA-approved gel system, contains 8.5% DOX and is supplied as a two-syringe mixing system [10]. However, Tomasi C. *et al*. reported limited success with retreatment of molar furcation sites using 8.8% DOX gel, achieving closure in only 50% of type I and 17% of type II furcation sites [73].

The overall findings regarding MIN gel indicated no significant benefit over scaling and root debridement (SRD) alone, leading the authors to recommend further clinical trials to clarify its role as an adjunctive therapy [44]. Conversely, another study reported contrasting results, demonstrating notable improvements in clinical parameters and overall periodontal health using the same drug concentration [74]. Additionally, research has shown that MIN gel therapy not only enhanced periodontal outcomes but also improved glycemic control and increased serum adiponectin levels in patients with type 2 diabetes [75].

When applied locally, metronidazole (MTZ) gel maintained concentrations above 100 µg/mL within periodontal pockets for at least 8 hours, gradually declining to levels above 1 µg/mL at 36 hours [7, 10]. MTZ is also available as a bioabsorbable delivery system, in which MTZ benzoate is incorporated into a matrix of glyceryl mono-oleate and sesame oil [76]. Upon contact with gingival crevicular fluid, the gel forms reversed hexagonal liquid crystals that minimize leakage from the pocket and sustain drug levels above the minimal inhibitory concentration for extended periods [76, 77]. However, Bergamaschi *et al*. reported no significant differences in clinical or microbiological outcomes when MTZ gel or tablets were used adjunctively in periodontal therapy [78].

Minocycline in 2% MC form is encapsulated within a bioresorbable polyglycolide-co-dl-lactide polymer, which typically resorbs over approximately 21 days [7, 10]. The microparticles are inherently bioadhesive, eliminating the need for additional adhesives or dressings. Once placed in the periodontal pocket, exposure to gingival crevicular fluid initiates hydrolysis of the polymer, releasing minocycline over a period of roughly 14 days or longer before complete resorption [7, 10].

Nanoparticulate drug delivery systems offer several advantages over MC, microparticles, and emulsion-based systems, including superior dispersibility in aqueous media, controlled release profiles, and enhanced stability [7, 10, 28]. Their nanoscale size enables penetration into deep periodontal pockets that may be inaccessible to other delivery systems, providing uniform drug distribution over extended periods [7, 10, 20–22, 28]. These systems also improve drug absorption and bioavailability, allowing effective treatment with lower dosages.

Conclusion

Evidence suggests that local drug delivery (LDD) is an effective approach for administering medications directly to periodontal sites. When combined with SRD, LDD enhances treatment outcomes in localized periodontitis or in sites unresponsive to conventional mechanical therapy. By delivering higher drug concentrations locally with lower overall dosages, LDD reduces systemic side effects. Clinicians should also consider practical factors, including ease of handling, application time, and cost, which may affect the overall efficiency of these therapies. Currently, there is insufficient evidence to declare one LDD system superior to another. Therefore, further large-scale, multicenter randomized controlled trials with extended follow-up are warranted to evaluate and compare the efficacy of these antimicrobial delivery systems. Clinicians are advised to view LDD as an adjunct to conventional periodontal therapy to achieve optimal clinical outcomes.

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