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REVIEW ARTICLE

Supra and subgingival application of antiseptics or antibiotics during periodontal therapy

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1 | INTRODUCTION

Periodontal diseases are characterized by inflammatory processes that arise as a result of disruption of the balance in the oral ecosystem (dysbiosis) characterized by an altered diversity and relative proportions of the microbial biofilm species. The factors that can lead to dysbiosis are poor oral hygiene, the presence of certain bacteria, certain lifestyles, inadequate nutrition and toxic habits such as smoking tobacco.[1–5] Recovery of the balance leads to the recovery of health (symbiosis). Treatment of periodontitis aims at controlling the size of periodontal pathogenic microbiota and includes mechanical debridement of root surfaces to disrupt the supra and subgingival dental biofilm. However, mechanical control of the microbial biofilm has some shortcomings including limited compliance,[6–10] tendency to reacquire baseline biofilm levels,[10] limited dexterity in certain cases[11] and lack of control of other non-dental biofilms on the tongue or tonsils.[12,13] Additionally certain periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, persist after mechanical treatment.[14–17] For this reason, measures adjunctive to supra and subgingival instrumentation have been proposed to compensate for the limitations of mechanical control.

In the S3 level clinical guideline for the treatment of patients with periodontitis Stages I–III published by the European Federation of Periodontology (EFP)[18] a stepwise approach has been established. It includes initially a first supragingival dental biofilm control, adjunctive therapies for gingival inflammation and risk factor control, a second step for subgingival biofilm and calculus control, and a third therapy step of repeated subgingival instrumentations or periodontal surgery, followed by supportive periodontal care with supragingival dental biofilm control, adjunctive therapies for gingival inflammation and risk factor control. Therefore, the main aim of this article is to review in a narrative manner the existing literature regarding the adjunctive use of chemical agents (antiseptics or antibiotics) locally (subgingivally) and topically (supragingivally) during the different steps in periodontal therapy performed in Europe.

2 | ANTISEPTICS

According to the glossary for the Centers for Disease Control and Prevention (CDC), an antiseptic agent is defined as a "substance that prevents or arrests the growth or action of microorganisms by inhibiting their activity or by destroying them. The term is used especially for preparations applied topically to living tissue". Antiseptics should be distinguished from disinfectants, which refers to agents "that eliminate many or all pathogenic microorganisms except bacterial spores on inanimate objects".

Antiseptics available for the chemical control of dental biofilm can be classified according to their effects as[19]:

- Antimicrobial agents: are those substances that have demonstrated a bacteriostatic and/or bactericidal capacity in "in vitro" studies.
- Reducing agents/plaque inhibitors: are those substances with either a quantitative or a qualitative effect on dental biofilm, which may or may not be sufficient to have an effect on gingivitis or caries.
- Antiplaque agents: are substances that affect the dental biofilm sufficiently to show a benefit in the control of gingivitis and/or caries.

All these products may be applied either topically (supragingivally applied) or locally (subgingivally delivered). The topical application of antiseptic agents refers to their use in all niches at the same time (tongue, tonsils, oral mucosa, ...) usually as rinses or dentifrices, with the general aim of controlling gingival inflammation by controlling oral biofilms. On the other hand, local application refers to the agent being delivered inside the periodontal pocket to exert their action specifically on the subgingival dental biofilm.

2.1 | Antiseptics: supragingival application

In the case of topical applications, products are usually provided as gels, rinses, dentifrices or sprays, with rinses and dentifrices being the most commonly used.

Rinses are composed of different ingredients such as colorants, flavorings, preservatives, stabilizers, and active agents. Carrying the active agents in mouthwashes allows easy use of the active agents and they are well accepted by patients. The active agent can reach hard-to-reach areas, such as the tonsils. The use of rinses is independent of the individual's ability to brush their teeth, but should not be recommended for young children who do not have the ability to rinse without swallowing the product. In addition, rinses have better pharmacokinetics than other vehicles such as gels or toothpastes, being able to achieve the therapeutic dose of the active agent more easily. Two systematic reviews[20,21] have found that their use is associated with better results in terms of reducing plaque and gingival indices compared to gels and toothpastes and in a meta-regression analysis, statistically significant differences were obtained when considering delivery format as a cofactor, with higher plaque reductions (%) for mouth rinses ($n = 7$ studies; Weighted mean differences [WMD] = −27.70%; 95% confidence interval [CI]: −35.60%; −19.70%; $p < 0.001$) compared with dentifrices ($n = 16$; WMD = −14.00%; 95% CI: −20.20%; −7.80%; $p < 0.001$).[22]

Dentifrices are made up of abrasives, detergents, thickeners, sweeteners, humectants, flavorings, colorants, and active agents. The formulation of active agents in toothpastes is more complicated due to the number of interactions with the other components present. The pharmacokinetics of the active agents is less predictable. In addition, the ability of the active agent to reach hard-to-reach areas is limited and is dependent on the individual's ability to brush their teeth properly. Although previous evidence has shown less efficacy in terms of plaque reduction when the active ingredient is delivered in the form of toothpaste[20–22] even in a non-brushing[20] and in a brushing model[21,22] they have the advantage that their use is extensive.

2.1.1 | Active agents

Throughout history, different products have been used as adjuncts to control gingival inflammation, such as enzymes, essential oils, metallic salts, quaternary ammonium compounds, bisbiguanides, amino alcohols, sodium hypochlorite, povidone-iodine, hexetidine, oxygenating agents, detergents, tin fluoride, different extracts of herbs, sanguinarine, etc. Currently, all agents must meet a series of requirements such as being proven to be safe and effective in clinical studies. These studies range from "in vitro" studies in which their antimicrobial capacity is evaluated for the minimum inhibitory concentration and minimum bactericidal concentration, to studies in artificial biofilms, to different "in vivo" studies that include antimicrobial tests, studies of plaque regrowth, experimental gingivitis studies and home use studies, usually in the format of randomized controlled clinical trials (RCTs). These different study types it is the latter that provides the most information on the effectiveness of a given substance. Additionally, information coming from different RCTs can be integrated by means of systematic reviews with or without meta-analyses. Antiseptics can be divided according to their proven efficacy. Some agents, such as hexetidine, metallic salts, sodium hypochlorite, enzymes, oxygenating agents, detergents, herbal products, povidone iodine or sanguinarine have not demonstrated efficacy in reducing biofilm and levels of gingival inflammation[21,22] and will therefore not be further explored in this chapter.

This section will review the evolution of the products currently in use in the different steps of periodontal treatment and of those that, despite having been proven to be effective have been discouraged for different limitations. Information on each active agent is presented both in a descriptive manner and as figures (Figure 1) and tables, reporting on systematic reviews or RCTs performed in Europe during Steps 1 & 2 (Tables 1 and 2), Step 3 (Table 3) and supportive periodontal therapy (Table 4).

Chlorhexidine

Chlorhexidine was developed in the 1940s by Imperial Chemical Industries (ICI) in England for the purpose of fighting malaria, although it was never used for that purpose. The first use of chlorhexidine was for disinfecting skin wounds in 1854. In the dental field, it was first used as an antiseptic in endodontics. The study by Löe and Schiött in 1970[23] confirmed the effectiveness of chlorhexidine mouthwash as a plaque-reducing and anti-plaque product, since it reduced the levels of dental biofilm and levels of gingival inflammation. Chlorhexidine has been shown to have a broad spectrum of action against gram-positive bacteria, gram-negative bacteria, fungi[24] and certain types of viruses, such as the hepatitis B virus, herpes virus[25] and human immunodeficiency virus.[26] It has also shown

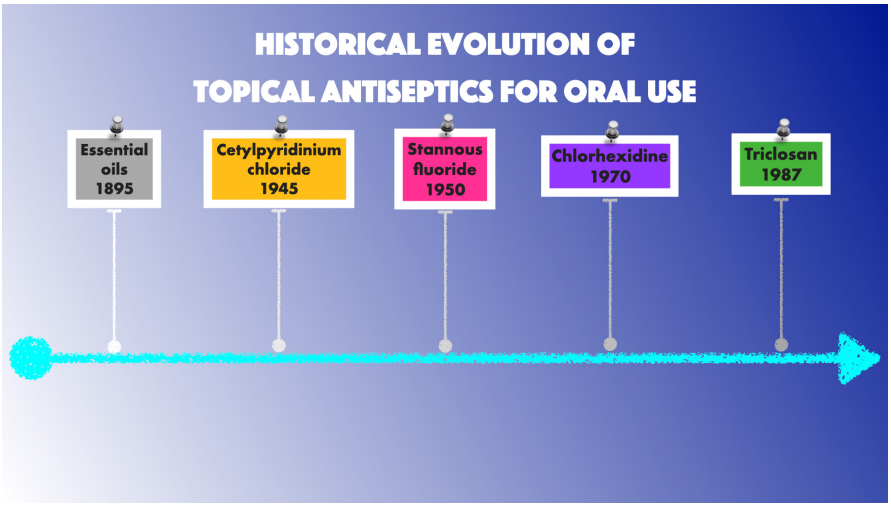


FIGURE 1 Timeline for topical antiseptics.

some penetrating power in artificial biofilm models.[27] Cumming and Loe[28] observed that if larger volumes were used, much lower concentrations of chlorhexidine were necessary. Subsequently, in a dose response study Cancro et al.[29] defined the optimal dose to obtain the greatest effect without increasing side effects. This optimal dose consists of 20 mg chlorhexidine per day, which is achieved by using 10 mL of 0.20% chlorhexidine mouthwash for 30 s or 15 mL of 0.12% mouthwash for 60 s.

Chlorhexidine is a positively charged molecule that binds with the negatively charged sites on the cell wall. It destabilizes the cell wall and interferes with osmosis. The bacterial uptake of the chlorhexidine is very rapid, typically working within 20 s. In low concentrations it affects the integrity of the cell wall. Once the cell wall is damaged, chlorhexidine crosses into the cell and attacks the cytoplasmic membrane (inner membrane). Damage to the cytoplasm's delicate semipermeable membrane allows leakage of components leading to cell death.[30–33] In high concentrations chlorhexidine causes the cytoplasm to congeal or solidify.[34] It is concluded that in clinical use chlorhexidine achieves plaque inhibition as a result of an immediate bactericidal action during application and a prolonged bacteriostatic action as a result of adsorption by the pellicle coated enamel surface.

Chlorhexidine maintains its antimicrobial effect in the oral cavity for more than 12 h[35] and due to its ability to bind to oral tissues, it can later progressively desorb.[36–38] Apart from its antimicrobial activity chlorhexidine is effective by interfering with the adhesion of bacteria to the tooth surface,[39] by producing glucans involved in adhesion by bacteria.[40]

Chlorhexidine has been marketed both as a mouthwash and as a toothpaste or gel. The first study on the use of chlorhexidine in toothpaste was carried out in 1973.[41] However, the first 6-month home use study was conducted in 1993[42] with 1% chlorhexidine and later[43] with 0.4% chlorhexidine and 0.34% Zinc, both with good results in terms of plaque and gingival inflammation control and in the case of Sanz et al.[43] with fewer side effects than chlorhexidine mouthwash. In their 6-month home use study, Rathe et al.[44] found that a 0.05% chlorhexidine digluconate and 0.8% aluminum lactate toothpaste with 1400 ppm aluminum fluoride and the corresponding control without chlorhexidine and aluminum lactate exhibited no statistically significant differences with regard to plaque index and the development of calculus and staining, but a statistically significantly lower gingival index compared with the control group ($p = 0.001$).

Chlorhexidine mouthwashes have been widely used in *Step 2 of periodontal treatment*. As early as 1976[45] better results after performing scaling and root planing (SRP) in the group of patients who used a 0.2% chlorhexidine mouthwash were observed. A systematic review[46] revealed a positive effect for both probing depth (PD) and clinical attachment levels (CAL) with the use of chlorhexidine as an adjunct to SRP, with a significant effect on PD at 40–60 days ($n = 2$ studies; 0.3 mm; 95% confidence interval (CI), 0.08–0.58 mm; $p = 0.010$) and 180 days ($n = 3$ studies 0.24 mm; 95% CI; 0.02–0.47 mm; $p = 0.035$) of follow-up. The results of the meta-analysis for CAL were favorable for chlorhexidine but not statistically significant ($p > 0.05$).

The main side effects observed after the use of products containing chlorhexidine during Step 2 of therapy are:

- Stains on the teeth and on the dorsum of the tongue.[47] To overcome this side effect during the last decades an anti-discoloration agent (ADS) was added into a chlorhexidine solution in order to avoid the mostly brownish deposits. Two agents with a synergizing action were claimed to interfere with the mechanisms that cause pigmentation without reducing antiplaque activity.[48] While numerous studies have found that the propensity of chlorhexidine to produce staining in vitro and in vivo was correlated with its effectiveness against plaque,[49–51] clinical studies with non-staining chlorhexidine solutions showed heterogeneous results. Arweiler et al.[52] found a significantly lower antibacterial effect compared to a conventional 0.2 cholrhexidine solution in a 4-day plaque regrowth design, and Li et al.[53] concluded that chlorhexidine with an ADS did not prevent plaque or gingivitis development and showed no superior effect over a placebo product. A recent systematic review[54] found a moderate quality evidence from

TABLE 1 Studies dealing with rinses during steps 1 & 2 of periodontal therapy.

Author	Year	Countries	Study design	Debridement	Test	Control	Application	Sample size	Follow up (months)	Authors' conclusions
Alshehri et al.[82]	2015	Saudi Arabia	RCT parallel	NR	EOs	None	2/day, 10 mL, 60 s, 6 weeks	120	3	EO-based oral rinses when used as adjuncts to conventional SRP are useful in the treatment of periodontal inflammation in smokers as compared to when SRP is used alone
Azad et al.[83]	2016	Germany	RCT parallel	FM in 2 sessions in 24 h	CHX, 0.20% + EOs	CHX, 0.20% + Placebo	CHX: 2/day, 60 s, 7 days EOs: 5 drops in water, 60 s, 14 days	64	6	The adjuvant use of a rinse containing EO has a positive effect on the course of treatment in periodontitis. The antibacterial effects should be outlined especially on *Fusobacterim nucleatum*
Garcia-Gargallo et al.[108]	2017	Spain	RCT parallel	FM in 2 sessions in 1 week	0.12% CHX and 0.05% CPC_new formulation 0.03% CHX and 0.05% CPC	0.12% CHX + 0.05% CPC	15 mL during 30 s, every 12 h, 4 weeks	20 20	1	The newly formulated 0.12% CHX and 0.05% CPC rinse, in conjunction with SRP, resulted in larger reductions of plaque levels, without showing more adverse effects, when compared to the other two rinses
da Costa et al.[46]	2017	Brazil	SR ($n = 6$ studies)	By quadrantor FM	CHX 0.12%–0.20%	Without the use of mouthwash or with placebo	Various aplications, during 4–9 weeks	241	1–6	Adjunctive use of CHX rinse with mechanical SRP resulted in slightly greater PD reduction than did SRP alone. Clinicians must consider the small additional gain in PD reduction, and potential for tooth staining

Abbreviations: CHX, Chlorhexidine; EOs, Essential oils; FM, Full-mouth; NR, Not reported; PD, probing depth; RCT, randomized clinical trial; SR, Systematic review; SRP, scaling and root planing.

TABLE 2 Studies dealing with dentifrices during steps 1 & 2 of periodontal therapy.

Author	Year	Countries	Study design	Debridement	Test	Control	Application	Sample size	Follow up (months)	Authors' conclusions
Kerdvongbundit et al.[135]	2003	Thailand, USA	RCT parallel	By quadrant	Triclosan/copolymer/fluoride	Fluoride	2/day/1 min/96 weeks	60	24	Oral hygiene regimen including a triclosan/copolymer/fluoride dentifrice may sustain the short-term effect of non-surgical periodontal therapy in smokers
Pera et al.[134]	2012	Brazil	RCT parallel	FM	Triclosan/copolymer/fluoride	Placebo with fluoride	≥3/day/NR/24 weeks	30	6	It could be concluded that triclosan/copolymer-containing dentifrices promote additional clinical benefits to one-stage FM in the treatment of periodontitis
Hrishi et al.[330]	2016	India	RCT parallel	FM	Green tea dentifrice	Fluoride and triclosan-containing dentifrice	2/day/2–5 min/4 weeks	30	1	The results of the present study assert the use of green tea dentifrice as an adjunct to SRP during the active and healing phases following periodontal therapy, thereby enhancing the clinical outcomes

Abbreviations: CHX, Chlorhexidine; EOs, Essential oils; FM, Full-mouth; NR, Not reported; PD, probing depth; RCT, randomized clinical trial; SR, Systematic review; SRP, scaling and root planing.

non-brushing studies that the addition of an ADS to chlorhexidine mouth rinses reduces tooth surface discoloration and does not appear to affect its properties in respect of gingival inflammation and plaque scores. In brushing studies there was also moderate quality evidence that ADS does not affect the anti-plaque and anti-gingivitis efficacy of chlorhexidine.

- Alterations in taste. In 1984, Botta et al.[55] described alterations in taste after the use of a chlorhexidine gel. Subsequently, Marinone and Savoldi[56] described how the alterations occur primarily in the perception of the salty taste and the bitter taste after the use of chlorhexidine mouthwashes at different concentrations.
- Mucosal erosion. Almqvist and Luthman[57] described the appearance of ulceration in the oral mucosa after the use of a 1% chlorhexidine gel and meticulous oral hygiene.
- Increased calculus formation.[42]
- More rarely hypersensitivity reactions[58–60] and parotid swelling have been found.[47]
- Although in the first studies on chlorhexidine mouthwashes resistance to it was not observed,[61] in recent years the appearance of resistance has been seen when certain types of bacteria are exposed (*Enterobacter* spp., *Pseudomonas* spp., *Proteus* spp., *Providencia* spp., and *Enterococcus* spp., *Klebsiella pneumoniae* at sublethal doses)[62] and the possibility of cross resistance with certain antibiotics (tetracycline, gentamicin, meropenem) in a hospital setting with the use of soap for hand washing.[63] Given that it is possible that chlorhexidine reaches sublethal doses inside the oral biofilm there is the possibility of cross resistance when using chlorhexidine mouthwashes,[64] which has not been shown so far in clinical application. Therefore it is necessary to restrict its use to applications that have shown a benefit for the patient, in the right doses and used correctly.
- As regards its use during pregnancy, in the package inserts of chlorhexidine solutions with concentrations ≥0.1%, which are approved as medicinal products in Europe, it is stated that "there is no sufficient experience or studies on the safety of use during pregnancy and lactation. Therefore chlorhexidine should be used with special caution". However there is a meta review in the scientific literature that includes 5 studies in which pregnant women used chlorhexidine rinses as part of periodontal therapy.[65] No serious side effects were reported. It was even concluded that daily use of chlorhexidine mouth rinses was associated with a reduction in preterm births.[66] In conclusion it is up to the dentist to carefully evaluate the recommendation.

Chlorhexidine has also been used in *Step 3 of periodontal therapy*. A chlorhexidine dressing was first used by Asboe-Jorgensen.[67] Subsequent studies demonstrated less plaque accumulation and less gingival inflammation after periodontal surgery procedures,[68] although in an in vitro study Mariotti and Rumpf[69] found some toxicity of chlorhexidine on fibroblasts and collagen production, which could compromise healing after surgical procedures. However, several systematic reviews have shown the benefit of using a chlorhexidine mouthwash after surgical periodontal procedures. Chyet et al.[70,71]

TABLE 3 (a) Randomized clinical trials dealing with the use of rinses during step 3 of periodontal therapy. (b) Systematic reviews dealing with the use of rinses during step 3 of periodontal therapy.

(a)

Author	Year	Countries	Study design	Test	Control	Application	Sample size	Follow-up	Authors' conclusions
Zambon[84]	1989	USA	RCT cross over	EOs	Saline solution	3/day, 20 mL, 30 s, 28 days	25	28 days	Use of an antimicrobial mouthrinse may be an effective aid in early healing of gingival flap surgery wounds.
Trombelli[331]	2018	Italy	RCT parallel	0.2% CHX + 0.2% HA + 0.2% ADS	CHX 0.2%	3/day, 10 mL, 60 s, 21 days	35	21 days	Postsurgery plaque control based on either CHX or CHX + HA + ADS mouthrinses results in optimal plaque control and quality of early gingival healing along with limited tooth and tongue staining
Katsaros[86]	2020	USA	RCT parallel	EOs, CHX 0.12%, 5% CHX, and 10% EO	Water	2/day, 15 mL, 30 s, 3 weeks	61	21 days	Full strength concentrations of CHX and EO were not shown to have any detrimental effects on healing after traditional periodontal surgery, at the end of the observation period. CHX provided the best level of plaque control when compared to the other four rinses that were used in this study
Collins[332]	2020	Dominican Republic, Chile; USA	RCT parallel	Sodium chloride (salt) water-based rinse	CHX 0.12%	2/day, 15 mL, 60 s, 1 week	37	3 months	Use of saline rinse after minimal invasive periodontal flap surgery has similar clinical and anti-inflammatory properties as CHX mouth rinse and can be used regularly at earlier stages of wound healing.

(b)

Author	Year	Countries	Test	Control	Weeks of use	Patients	Follow up	Studies	Authors' conclusions
Chye[70]	2019	Australia, Italy	CHX 0.1%, CHX 0.2%	Placebo	1–6 weeks	99	1 week to 3 months	4	Both 0.1% and 0.2% chlorhexidine rinses are effective in preventing plaque formation and in reducing gingival inflammation during the early healing period after periodontal and implant surgery.
			Alcohol-free CHX	CHX	2 weeks	20	4 weeks	1	The presence of alcohol in the CHX mouthwash does not seem to influence the antiplaque effect
			CHX with ADS system	CHX	1–2 weeks	108	2 weeks	2	The post-operative use of CHX rinse with an anti-discoloration system showed effectiveness similar to the traditional CHX rinse
			Other CHX	CHX	2–4 weeks	125	2–12 weeks	3	Better patient acceptance was reported with newer CHX mouthwash formulations and concentration below 0.2%.

TABLE 3 (Continued)

(b)

Author	Year	Countries	Test	Control	Weeks of use	Patients	Follow up	Studies	Authors' conclusions
Soldierer[71]	2019	Switzerland	CHX (0.12%–0.2%)	Placebo	1 week to 3 months	82	1–6 weeks	4	CHX rinsing helps to reduce plaque accumulation and gingival inflammation after periodontal and implant surgery
			Alcohol-free CHX	CHX	1 week to 3 months	62	2–4 weeks	2	One study not find any significant differences in plaque inhibition or amount of staining between the two solutions. The other find significant superior plaque control of alcohol-based CHX over alcohol-free CHX
			CHX with ADS system	CHX	1 week to 3 months	100	2 weeks	2	The adjunct of ADS could be of value after surgery where patient compliance is very important
			Other CHX formulations	CHX	1 week to 3 months	125	2–12 weeks	3	These new formulations have similar effects on plaque index and healing with less adverse effects

Abbreviations: ADS, antidiscoloration system; CHX, chlorhexidine; EOs, essential oils; FM, Full-mouth; HA, hyaluronic acid; NR, Not reported; PD, probing depth; RCT, randomized clinical trial; SR, Systematic review; SRP, scaling and root planning.

found that all studies reported significantly less plaque accumulation when using chlorhexidine rinses compared to the placebo groups. In terms of bleeding on probing (BOP), reductions ranged from 0% to 73% after 1 week. For wound healing and epithelialization, no statistically significant differences could be found, although chlorhexidine showed consistently better epithelialization. In terms of PD, no beneficial long term effect could be seen from postoperatively administered chlorhexidine over placebo rinsing (two studies). Significantly more staining ($p = 0.017$) after its use was noted.

Normally the side effects associated with the use of chlorhexidine after surgical procedures are relatively well accepted by patients, since they are of short duration. Also within the scope of Step 3, alternative chlorhexidine formulations with hyaluronic acid or herbal extracts primarily to promote healing but also to minimize side effects such as staining have been studied. Similar results were observed in these studies regarding plaque levels and healing with the chlorhexidine mouthwashes used as positive controls and although there are fewer side effects, these were not completely eliminated.[71]

Chlorhexidine has also been used during *supportive periodontal care*. Patients with periodontitis should enter a periodontal maintenance program once they have been adequately treated[72,73] to prevent disease recurrence and progressive attachment loss. The use of mouthwashes and/or toothpastes with chlorhexidine has been proposed together with the periodontal maintenance program to improve control of dental biofilm and prevent future attachment loss.[22]

While common side effects of chlorhexidine have already been mentioned within the scope of Steps 1–3, long term effects have to be considered especially in supportive periodontal therapy. In this context a recent finding should be further examined. It was found that products with chlorhexidine could decrease oral bacteria that are involved in the metabolism of nitric oxide which could produce a rise in the blood pressure of patients,[74] although later studies have found greater effect in the suppression of nitrites when performing SRP in periodontal patients than in the use of a chlorhexidine mouthwash.[75] Nevertheless, the use of chlorhexidine products in periodontal maintenance programs should be reserved for those cases in which it is really necessary due to the impossibility of achieving adequate control of the dental biofilm by other means.

Essential oils

Although most of the studies on this product come from the USA, some of the studies that explain its effects on the reduction of gingival inflammation[76] or on its side effects[77] have been undertaken in Europe.

Antiseptic agents containing essential oils are mouth rinses based on thymol (0.06 g), eucalyptol (0.09 g), menthol (0.04 g), methyl salicylate (0.05 g) and benzoic acid 0.150 g in a hydroalcoholic base (usually with 28.4%).

Essential oils were first used as a surgical disinfectant in 1879. A special formulation of the above mentioned compounds was the first mouthwash marketed in 1895 for the treatment of halitosis in the USA and named in honor of Joseph Lister, "the father of antiseptic

TABLE 4 (a) Randomized clinical trials dealing with the use of rinses during supportive periodontal maintenance. (b) Systematic reviews dealing with the use of rinses during supportive periodontal maintenance.

(a)

Author	Year	Countries	Study design	Test	Control	Application	Sample size	Follow up	Authors' conclusions
Cullinan et al.[136]	2003	Australia, UK	RCT parallel	Triclosan, copolymer and sodium fluoride	Pacebo	Dentifrice, 240 weeks	504	60 months	In a normal adult population, unsupervised use of a triclosan/copolymer dentifrice is effective in slowing the progression of periodontal disease
Guarnelli et al.[153]	2004	Italy	RCT crossover	AmF/SnF_2	Placebo	Rinse, 2/day, 10 mL, 12 weeks	18	12 weeks	The use of a AmF/SnF_2 rinse as an adjunct to conventional mechanical oral hygiene procedures in periodontitis patients was effective in controlling the supragingival plaque levels
Santos et al.[109]	2004	Spain	RCT parallel	No alcohol 0.05% CHX and 0.05% CPC	Placebo	Rinse, 2/day, 15 mL, 60 s, 2 weeks	27	2 weeks	The results of the present study demonstrate that the test product is effective in reducing plaque levels
Quirynen et al.[110]	2005	Belgium	RCT parallel	No alcohol 0.05% CHX and 0.05% CPC	Placebo and positive control (CHX 0.2% with alcohol)	Rinse, 2/day, 24 weeks	48	6 months	The new CHX 0.05%, CPC 0.05% solution has an antiplaque effect comparable with that of a 0.2% CHX alcohol solution, but with less side effects
Escribano et al.[111]	2010	Spain	RCT parallel	No alcohol 0.05% CHX and 0.05% CPC	Placebo	Rinse, 2/day, 10 mL, 30 s, 12 weeks	47	3 months	The test rinse demonstrated efficacy in reducing plaque levels and bleeding scores. These effects may improve the clinical conditions of treated periodontitis patients with an inadequate mechanical plaque control
Cosyn et al.[89]	2013	Belgium	RCT parallel	EOs	Placebo	Rinse, 2/s, 20 mL, 12 weeks	44	3 months	Plaque and gingivitis levels improved over time irrespective of the group, implying no additional benefit of EOs

TABLE 4 (Continued)

(a)

Author	Year	Countries	Study design	Test	Control	Application	Sample size	Follow up	Authors' conclusions
Seymur et al.[137]	2017	Australia, New Zealand	RCT parallel	Triclosan	Placebo	Dentifrice, 2/day, pea-sized amount/240 weeks	381	5 years	Data suggest that the use of triclosan/copolymer-toothpaste significantly slowed the progression of periodontitis in patients with CVD, but that it had little influence on key subgingival periodontopathic bacteria in these patients, suggesting that the clinical efficacy may be the result of a local anti-inflammatory effect
Azaripour et al.[333]	2016	Germany, the Netherlands	RCT parallel	Aluminiun triformate	Placebo	Rinses, 3/day, 30 s, 1 week	40	1 week	ATF rinse solution appears to be a promising adjunct to mechanical tools in the periodontal maintenance phase in our short-term pilot clinical trial. The current study shows that the ATF rinse solution is well accepted by patients and does not have major and long-lasting side effects
Stewart et al.[138]	2020	Brazil, USA	RCT parallel	0.3% triclosan, 2.0% PVM/MA copolymer	Placebo toothpaste	Dentifrice, 2/day, 60 s, 96 weeks	88	24 months	A toothpaste containing 0.3% triclosan was more effective than a regular fluoride toothpaste in improving the periodontal clinical condition around natural teeth of periodontally healthy subjects enrolled in a regular maintenance program for 2 years
Kaur et al.[334]	2021	USA	RCT parallel	2.6% EDTA	Positive control 0.454% stannous fluoride	Dentifrice, 2/day, pea size amount, 24 weeks	65	6 months	The results of this clinical study show that Stage I and II periodontitis patients can achieve significant PD reductions, reduce the level of inflammation and improve their periodontal health by using the test dental gel as a home care dentifrice during SPT and/or between scheduled SPT visits

(Continues)

TABLE 4 (Continued)

(b)

Author	Year	Countries	Test	Control	Format	Weeks of use	Sample Size	Studies	Author's conclusions
Van der Weijden et al.[91]	2015	The Netherlands	Various	No control or placebo	Rinse	≤4–24 weeks	NR	9	Evidence suggests that a mouthwash containing CHX is the first choice. The most reliable alternative for plaque control is EO. No difference between CHX and EO with respect to gingivitis was observed
James et al.[335]	2017	Ireland, UK	CHX rinse 0.05%, 0.06%, 0.1%, 012%, 0.2%	Placebo/control rinse	Rinse	4–24 weeks	5345	51	There is high-quality evidence of reduction in gingivitis in individuals with mild gingival inflammation on average that was not considered to be clinically relevant. There is high-quality evidence of a large reduction in dental plaque with CHX rinse used as an adjunct to mechanical oral hygiene procedures for 4–6 weeks and 6 months. There is no evidence that one concentration of CHX rinse is more effective than another. There is insufficient evidence to determine the reduction in gingivitis associated with CHX rinse use in individuals with moderate or severe levels of gingival inflammation. Rinsing with CHX rinse for 4 weeks or longer causes extrinsic tooth staining. In addition, other adverse effects such as calculus build up, transient taste disturbance and effects on the oral mucosa were reported in the included studies
Figuero et al.[22]	2020	Spain, Singapore	Various	No control or placebo	Rinse, dentifrice	≥24	6424 T 6558 C	70	Principal findings: Adjunctive antiseptics in both mouthrinse and dentifrice formulations were effective in reducing gingival, bleeding and plaque indices, in patients with gingivitis (with or without attachment loss due to periodontitis) Practical implications: Adjunctive antiseptic mouthrinses and dentifrices can help to reduce gingival, bleeding and plaque indices

Abbreviations: ATF, Aluminum triformate; CHX, Chlorhexidine; CPC, Cetylpyridinium chloride; EOs, Essential oils; PD, Probing depths; PVM/MA, Copolymer of methyl vinyl ether and maleic anhydride; RCT, randomized clinical trial; SPT, Supportive periodontal therapy.

surgery". Later, in 1983, its antiplaque properties were observed[78] and in 1987 it received the approval of the American Dental Association as a mouthwash with antiplaque action.

The main effect on bacteria is the disruption of the bacterial wall, although they also produce inhibition of bacterial enzymes and could also affect the lipopolysaccharides of gram-negative bacteria.[79] Essential oils also appear to have some anti-inflammatory action due to their antioxidant activity.[76]

Side effects described include a burning sensation after its administration and it can produce a certain dental staining. Initially its high alcohol content was claimed to be associated with an elevated risk of oral cancer but more detailed studies have not linked essential oil mouthrinse with this disease.[77,80,81]

Clinical studies dealing with the use of essential oils during *Step 2 of therapy* have been mainly carried out outside of Europe. In those studies, an improvement in clinical parameters when essential oils are used after performing SRP[82,83] has been demonstrated.

In Europe, they have mainly been studied during *Step 3 of periodontal therapy*[84] reporting their efficacy in reducing plaque level (mean difference = 28.9%) and improving wound healing at day 7 as measured by edema, although no significant differences in terms of gingival index scores or bleeding were found at any time. Originally it was thought due to in vitro studies[85] that this product could interfere with fibroblasts and as a consequence, affect wound healing after surgical procedures, but the study by Katsaros et al.[86] shows that this assumption is no longer supported.

Essential oils have been used primarily to reduce the levels of plaque and gingival inflammation in the general population.[87,88] A clinical study carried out in Europe[89] and various systematic reviews[22,90,91] also carried out in Europe, have shown the usefulness of the product to reduce the levels of plaque and gingival inflammation in patients undergoing *periodontal maintenance*.

Cetylpyridinium chloride

Cetylpyridinium chloride (CPC) is a monocationic quaternary ammonium compound with a substantivity of 3–5 h.[92] Its mechanism of action is through the interference of its hydrophilic part with the cell membrane, producing a loss of cellular components, alteration of cellular metabolism and death of the bacteria.[93,94] Since only part of the molecule is the active part it can be inactivated if it is not formulated correctly, which may explain the heterogeneity of the results of the different studies found in various systematic reviews.[95,96]

The first to demonstrate the effect of CPC on bacteria in the oral cavity was Lee Huyck in 1945.[97] Safety in its use has been demonstrated at concentrations between 0.045% and 0.1%.[92,98–103] After its use no changes in the oral microbiota or overgrowth of opportunistic species have been demonstrated.[104–106] Its side effects are similar to those of chlorhexidine, tooth and tongue staining, transient gingival irritation and aphthous ulcers but with less frequency and intensity.[107]

Cetylpyridinium chloride formulated in a 0.05% mouthwash together with 0.12% chlorhexidine has been used in *Step 2 of periodontal treatment* observing a mean reduction in probing depth of 0.68 mm (SE = 0.17) at 1 month.[108]

In Europe, it has also been used during *periodontal support treatment* formulated at 0.05% together with 0.05% chlorhexidine.[109–111] Statistically significant differences in terms of reduction in plaque and gingival indexes were reported, without significant differences in probing depth.[91,95,96]

Triclosan

Triclosan is a chlorinated bisphenol (2,4,4′-trichloro-2′-hydroxydi phenyl ether), used as an antiseptic in many products for hospital use and in various consumer products such as soaps, toothpastes, mouthwashes, deodorants, plasters, bandages, and household products.

Triclosan acts by altering the cytoplasmic membrane through the inhibition of the FabI gene responsible for the synthesis of fatty acids in the membrane.[112] It can also produce a leak of potassium ions through the membrane[113] and has an anti-inflammatory effect by inhibiting lipoxygenase and cyclooxygenase, producing a reduction in the production of prostaglandins and leukotrienes.[114–116] The appearance of bacterial resistance after the use of triclosan has not been described.[117–119]

Triclosan was developed in 1960. It was first used in hospitals for hand washing[120] and the first studies on its effect on bacteria in the oral cavity date from 1987.[121]

The following side effects associated with the use of triclosan have been described:

- Endocrine disruptor.[122]
- Could induce metastasis in breast cancer.[123]
- Environmental risk. Traces of triclosan have been found in much of the river water. The concentration of triclosan in water can inhibit algae photosynthesis and affect river ecosystems.[124–126]
- It could increase calcium levels in neurons and could affect mental development according to an in vitro study.[127]
- It could react with chlorine in treated drinking water and produce a carcinogenic compound.[128]
- It has been observed that it is capable of accumulating on the nylon bristles of toothbrushes with subsequent release.[129]

Due to the risks associated with its use the Florence declaration of 2017[130] recommends avoiding the use of triclosan, except in cases where it provides a certain benefit for the individual's health based on evidence.

Triclosan formulated as a 0.2% mouthwash has shown limited efficacy in different studies[27,131] and systematic reviews.[90,95,132] Formulated in toothpaste together with polyvinyl-methyl ether maleic acid copolymer or zinc citrate or pyrophosphate, to improve its efficacy and substantivity, it has demonstrated its effectiveness in reducing the amount of dental biofilm and bleeding in various systematic reviews.[21,90,95,133]

In *Step 2 of periodontal treatment*, it has been used in the form of toothpaste showing greater gains in CAL, lower levels of dental

biofilm and gingival bleeding[134] and a greater reduction in the percentage of pockets greater than 3 mm.[135]

Its use during *supportive periodontal treatment* has also been recommended as a toothpaste,[136–138] with lower levels of plaque and gingival indices and lower attachment loss.

Stannous fluoride

Stannous fluoride has been used since the 1940s in gels, toothpastes and mouthwashes. The first studies on the use of stannous fluoride for caries prevention were carried out in 1950 in rats[139] and in 1955 in humans.[140] It is difficult to formulate in oral hygiene products due to its hydrolysis in the presence of water forming insoluble stannous compounds that are not effective. In 1990 it was discovered that it can be stabilized by adding different polyphosphates such as sodium hexametaphosphate or zinc phosphate.[141]

Stannous fluoride inhibits bacterial growth by interfering with bacterial metabolism, reducing the ability of bacteria for adhesion, cohesion and acid production.[142–144,230]

Its main side effects are its astringent taste and causing dental stains.[145,146]

Different formulations have been studied, those stabilized with polyphosphate or amine fluoride being the most frequently studied. The use of stannous fluoride produces a reduction in the number of caries[147–149] and reduces the levels of dental biofilm and gingival inflammation, as has been shown in different systematic reviews.[95,146,150–152] The reported effect on the reduction in plaque index is small, with weighted mean differences (WMD) ranging from 0.16[95] to 0.28[150] when compared to controls. However, the effect on the reduction in the gingival index is greater and clinically relevant with WMD ranging from 0.15,[146] 0.44[95] or 0.63.[151]

No RCT carried out in Europe in which stannous fluoride is used *during Step 2 or 3 of periodontal treatment* has been identified. Its use has been mainly during *periodontal maintenance* formulated in toothpastes and mouthwashes. Van der Weijden et al.[91] in a meta review found weak evidence for small or indistinct effects of stannous fluoride in the management of gingival inflammation. In the RCT by Guarnelli et al.[153] a mouth rinse containing a combination of AmF/SnF_2 demonstrated significantly lower plaque levels in test (0.64 [SD = 0.418]) compared to control mouth rinse (0.79 [SD = 0.362]; $p = 0.027$) although no significant differences were noted in the post treatment gingival index between groups. Since May 2022 there is no rinsing product with the combination of AmF/SnF_2 on the European Market.

2.2 | Antiseptics: administered subgingivally

In the scope of effective techniques or agents for managing supra and subgingival bacterial biofilm, subgingival irrigation is carried out either by professionals or self-performed by the patient. When complex subgingival biofilm is present within the pocket they should be cleaned regularly. While tooth brushing represents the most common oral hygiene method in western countries, its subgingival effect is very limited. It has been shown in former studies that brushing with two different techniques (Roll and Bass) was not able to transport experimental particles in the crevicular epithelium and underlying connective tissue in patients with periodontal disease.[154] By using irrigating devices in the same experiment carbon particles were detected in the crevicular tissue.[155]

Although the aim of these experiments was the exclusion of the spread of bacteria into tissues through toothbrushing and the proof that pressured water injection could force bacteria into the tissues, it can also be interpreted that toothbrushing has very restricted effect on subgingival areas which was later confirmed by Waerhaug.[156]

Thus it seems sensible to support subgingival mechanical biofilm management with antibacterial agents. Although they can be directly applied subgingivally their effect on the subgingival biofilm has some restrictions. Subgingival biofilm consists of adherent and planktonic bacteria, which often harbors more anaerobes than its supragingival counterpart. Moreover, it is often difficult for antibacterial agents to reach the periodontal pocket and its site of action in sufficient concentration to affect the biofilm. A further disadvantage is the gingival crevicular fluid flow, which is increased at inflamed sites and washes out applied agents within a short period of time.[30,157]

While the fluid flow limits the subgingival efficacy of agents they can even be inactivated by serum proteins in periodontal pockets. This is especially true for chlorhexidine which is the most common agent for subgingival irrigation. It was shown that it is inactivated by blood and serum,[158,159] and therefore the effects of chlorhexidine observed in the supragingival environment cannot be simply extrapolated to the subgingival milieu.

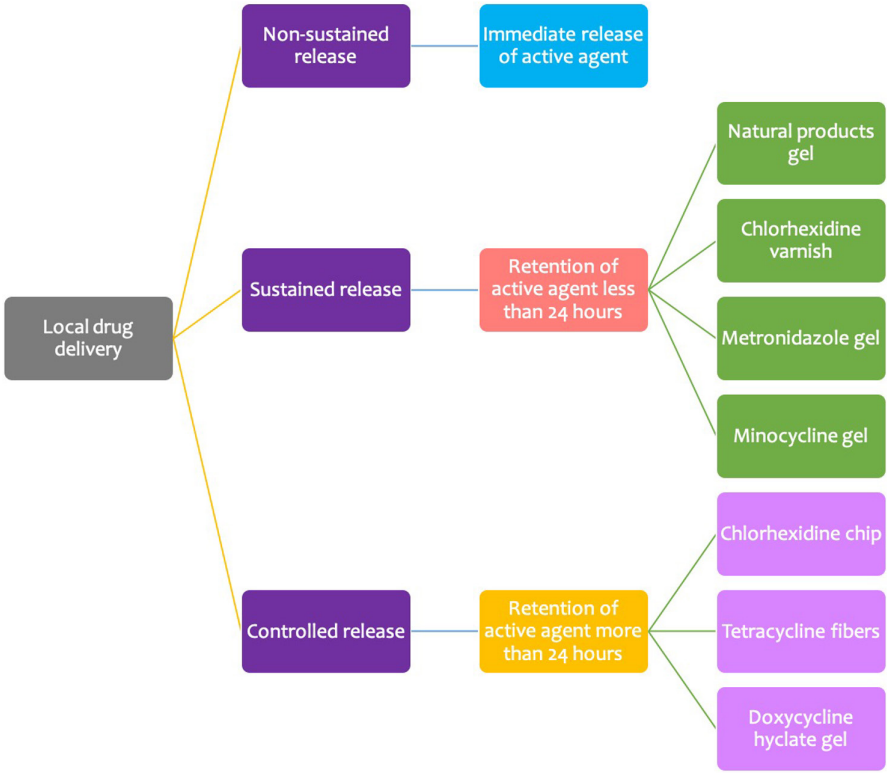
Most irrigation or lavage of pockets is administered professionally and aims to flush away unattached plaque or coronal bacteria to the supragingival margin, dilute plaque toxicity and to interfere with subgingival biofilm maturation in order to directly reduce pocket microbiota.[160] However as mentioned above it also creates the risk of forcing bacteria into the pocket or causing bacteraemia.[155]

Larner and Greenstein[161] stated that the presence of calculus due to lack of previous scaling and root planing, irrigator tip design (either side or end port cannula) and irrigation force (to minimize the potential of projecting bacteria into tissues) are factors that affect drug delivery. However they showed that under optimal conditions a penetration of 90% in pockets ≤6 mm and up to 80% in pockets 6.5–10.5 mm deep.

Several studies could not demonstrate significant differences between control solutions (sodium chloride) and other antibacterial agents (Chlorhexidine, PVPiodine) when used for subgingival irrigation during SRP (Step 2).[162,163]

The authors of an animal study in rats emphasized their agreement with the position of the American Academy of Periodontology (AAP) that there is insufficient evidence to indicate the routine use of subgingival irrigation as adjunct to periodontal treatment. No significant differences between the group treated with SRP and groups treated additionally with subgingival irrigation regarding bone support and epithelial migration were found.[164]

FIGURE 2 Local delivery systems.



Even when the patient administered chlorhexidine (2%) irrigation of deep pockets daily for 24 weeks after one episode of SRP, it did not enhance the effects compared to non-irrigated controls.[165]

Studies that yielded significant reductions of clinical parameters (plaque and bleeding indices) as well as of bacteria (as a mono-therapy with chlorhexidine, stannous fluorides, PVP iodine, tetrapotassium peroxydiphosphate rinses) often resulted in a quick rebound to baseline values within 1–8 weeks and no response to tissue invasive organisms (e.g. *Aggregatibacter actinomycetemcomitans*).

Alternative attempts to directly influence pocket microbiota by brushing a mix of sodium bicarbonate and hydrogen peroxide between the teeth and gingiva and leaving for 1 min, did not lead to significant benefits in reducing the microbiome of periodontal pockets.[166]

A systematic review[167] yielded only two RCTs that examined the efficacy of subgingival irrigation (SI) as an adjunct to SRP in patients with periodontitis. The authors point out that the studies were methodologically not perfect (mediocre quality) and had a risk of bias for any final conclusions to be reached. They concluded that there is insufficient evidence supporting the efficacy of SI as an adjunct to SRP in treating chronic periodontitis.

Although a recent study yielded significant reductions in PI, GI, PD, and colony-forming units from baseline to 30 days after subgingival irrigation with propolis extract versus 0.2% chlorhexidine as an adjunct to SRP in the treatment of periodontitis and patients in both groups showed slightly better results for chlorhexidine,[168] it should be kept in mind that there was no control group.

In summary, the main therapeutic effect of subgingival irrigation offers limited benefit as a professional application and in combination with SRP. It is not recommended to include it in a patient's daily home care regimen.[160] Self-administered, direct cleaning of pockets is either not possible or extremely difficult to perform and it does not represent a realistic approach.

3 | ANTIBIOTICS: SUBGINGIVALLY DELIVERED

Drug delivery systems (DDS) have drawn great attention and are considered as important adjunctive therapy for infectious diseases.[169,170] They are pharmaceutical formulations or devices that enable transport of pharmaceutical compounds including antibodies, peptides, vaccines, drugs and enzymes safely to their site of action at the desired body location and release contents at a predetermined therapeutic level for a fixed period.[171] DDS can be classified according to their physical state, location and route of administration and the rate of drug release.[172] Approaches for incorporating drugs into solid polymers began in the 1950s for agricultural products which were extended to include medicines in the mid-1960s.[173]

In view of the generally accepted principles for the treatment of infectious diseases, anti-microbial treatments in periodontics have been used along with mechanical debridement in the management of periodontal infection. Systemic administration and local drug delivery are both important methods for drug administration.[174] In the past half century systemically applied antimicrobials have been advocated for the treatment of severe forms of periodontitis. On the other hand, concern emerged in relation to the use of systemic antibiotics due to adverse effects including hypersensitivity,

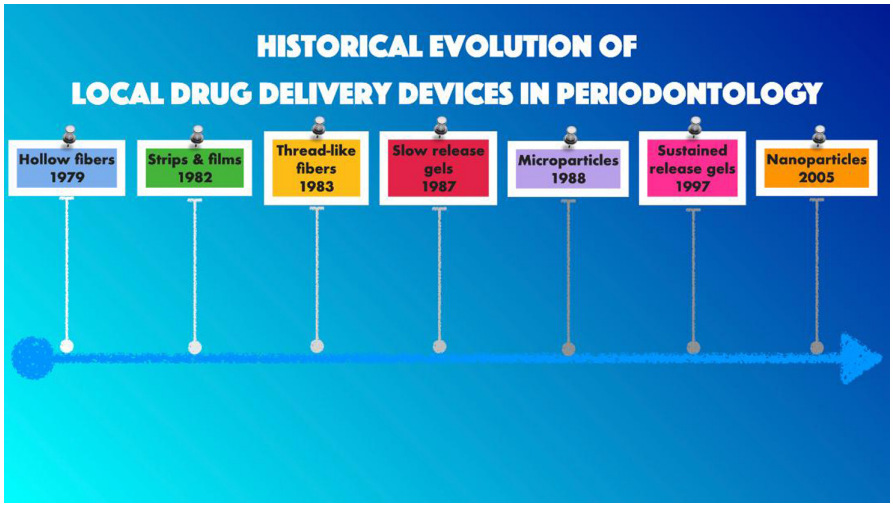


FIGURE 3 Historical evolution of local drug delivery devices in periodontology.

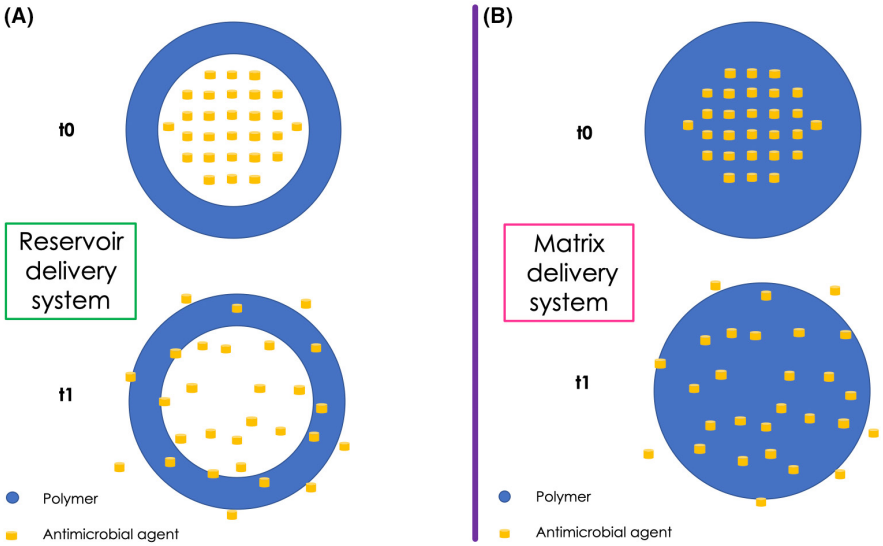


FIGURE 4 Reservoir versus matrix delivery systems.

gastrointestinal intolerance, acquired bacterial resistance, and drug toxicity.[175,176] Other drawbacks such as the failure to reach the site of infection and attain adequate concentration, poor tissue penetration, and lack of patient compliance would be markedly reduced if antimicrobial agents applied locally could be used.[174] In contrast to the systemic route, local application aims to deliver a high concentration of antimicrobial directly to the site of periodontal infection and facilitate the retention of a medicament for a required period to combat the microbial attack.[177] This method of drug delivery avoids most of the problems associated with systemic therapy. Local delivery when compared to systemic delivery reduces the risk of systemic adverse events minimizing its undesirable effects on non-oral systemic body sites, provides more constant and higher concentrations of drug at the location avoiding fluctuations in drug levels. All these factors make local drug delivery an ideal choice with excellent potential.[170] The local delivery of drugs provides 100 times higher therapeutic doses of an antimicrobial agent in the subgingival areas compared to the systemic drug regimen and prohibits development of drug resistant microbial populations at non oral sites.[174]

The temptation to place something in pockets goes back to 1913 when antiformin (sodium hypochlorite) was introduced into periodontal therapy for removal of pocket epithelium.[178] In the 1950s, antimicrobials were incorporated into dental cements and resins in order to provide local drug release of antimicrobials.[179] It has been suggested that antiformin may be able to sterilize the pocket.[180] The principle and local application of therapeutic agents in the treatment of periodontal infections was conceived by J. Max Goodson, a dentist and a pharmacologist in the middle of the 1970s.[181] Since its first inception various antimicrobial agents and local delivery systems have been attempted as an adjunct to traditional periodontal therapy.[182]

Kornman[183] introduced two terms relating to the concept of local delivery, "local delivery" and "site-specific delivery" which were used synonymously with "targeted delivery". Other important terms are "controlled-delivery" or "controlled-release". Either "topical drug delivery" or "controlled drug release" are means of applying drugs to a restricted region of the body termed as local drug delivery. But, the term "local delivery" is usually used to suggest more specific and targeted delivery of an agent at the site of required action. The mode

by which a drug is delivered to a specific site has a significant role on its efficacy. Based on the duration of action, local delivery into periodontal pockets has been classically categorized as "non-sustained", "sustained" or "controlled" release subgingival delivery. In "sustained subgingival release", drug delivery is for less than 24 h whereas in "controlled release" drug delivery is for more than 24 h[177,184,185] (Figure 2). Recently, Tan et al.[186] revised and modified those classifications of LDD in view of the introduction of new adjunctive agents including medical devices.

Topical application, a form of local delivery generally refers to delivery of an agent to an exposed surface. Drugs may be administered by topical delivery systems through various routes in the body such as skin, nose and vagina, formulated as solid and semi-solid dosage forms. Local antimicrobial agents can be used as part of home oral hygiene regimens or professionally applied as part of office-based treatment procedures.[177] Topical administration in the form of mouthwashes, dentifrices, dental gels, irrigation devices and professional administration into the pocket by means of syringes are routes for localized adjunctive pharmacological periodontal therapy. The clinical effectiveness of a pharmacological agent depends on three pharmacokinetic criteria; reaching the site of action, maintaining an adequate concentration there and remaining long enough for the intended pharmacological effect to occur.[181,185,187] As regards the ability to reach the site of action, agents in mouth rinses and supragingival irrigating solutions are unable to predictably reach the apical portions of periodontal pockets >5 mm.[188,189] Placing topical drug delivery into the oral cavity is challenging due to obstacles such as rapid washout of the active agent rapid removal due to continuous saliva flow and tongue movement and accidental swallowing[190] (see also Section 2.2).

Treating periodontal diseases using local drug delivery systems is based on the prospect of maintaining effective high levels of the drug in the periodontal pocket for a prolonged period of time to produce the desired clinical benefits.[183] The release of a drug from the application device and its distribution throughout the pocket is provided by gingival crevicular fluid (GCF), which acts as the leaching medium and greatly increases the clearance of the drug by the outward flow.[191] It has been estimated that the fluid present in a 5 mm periodontal pocket is replaced about 40 times/h.[187] Thus the concentration of a locally delivered antimicrobial agent is expected to decay according to an exponential equation with a half-life of elimination of about 1 min.[187] Such a high rate of clearance combined with the physical limitations of fitting a drug reservoir of adequate size in the periodontal pocket represent the major obstacles to maintaining effective concentrations of an antimicrobial agent for a long duration in the periodontal pocket.

Controlled delivery systems are designed to release a drug slowly on a consistent basis for more prolonged drug availability and sustained drug action.[184] There were various terminologies to denote the controlled and prolonged release of a drug in the past. They are commonly referred to as sustained-release, controlled-release, prolonged-release, timed-release, slow release, sustained-action, prolonged-action, or extended-action.[183] However the most commonly used terminologies are sustained release and controlled release. The best known controlled delivery systems are the scopolamine skin patches for motion sickness and the nicotine skin patches to aid smoking cessation.[192] The use of controlled drug release devices may well improve the antimicrobial efficacy in the periodontal pocket, with consequent clinical benefits.[186,193]

3.1 | Drug delivery systems in periodontics

The concept of using drug delivery devices in periodontal therapy dates back to 1979, but technology has advanced since then.[194–197] Various types of drug delivery devices in the form of fibers, gels, strips, films, biodegradable gels, solutions, vesicular systems, microparticles and nanoparticles have been developed[169,172] (Figure 3). The efficacy of drug delivery systems is mainly affected by the biological environment and the properties of the polymer and the drug itself.[198] Vast numbers of antimicrobial agents have been used so far in formulations of delivery systems such as tetracycline, doxycycline, minocycline, metronidazole, ornidazole, tinidazole, secnidazole, satranidazole, azithromycin, clarithromycin, ofloxacin, moxifloxacin, piperacilin clindamycin, amoxicillin/clavulanic acid, chlorhexidine, methylene blue, cetylpyridinium chloride and sanguinarine.[177,199–203] Some antimicrobial agents were chosen because of their substantivity properties.[204]

Earlier devices were nonbiodegradable and required the physical removal of the device from the pocket at the end of the treatment. Degradable devices have the great advantage of not needing to revisit a dentist to remove the device.[191,205] Naturally occurring polymers such as chitosan, cellulose, alginate and synthetic polymers such as poly(ε-caprolactone) (PCL), poly(D,L-lactide) (PLA), poly-(D,L-lactide-*co*-glycolide) (PLGA), poly-(vinylpyrrolidone) (PVP) and poly(vinyl alcohol) (PVAL) have been extensively investigated.[169,206,207] The drug seeps out of the device into the pocket in many different ways through solute diffusion, polymer matrix swelling, degradation and erosion of the polymeric material.[198] Drug delivery systems generally release and control drug release by diffusion, solvent activation and chemical reaction.[184]

Reservoir systems, reservoirs and matrices, are controlled by drug diffusion across a polymeric membrane. Solvent controlled matrix systems involve activation either by swelling of the polymer or osmotic effects.[184] In chemically controlled systems the rate of drug release is accomplished either by polymer degradation or chemical cleavage of the drug from a polymer.[208] The controlled release local delivery systems that have been used in periodontal care include either reservoirs without a rate-controlling system or reservoirs with a rate-controlling system.[183]

3.1.1 | Reservoir delivery systems

Reservoir type systems contain a compact drug core surrounded by a swollen or non-swollen polymer film (Figure 4). The membrane

thickness and the permeability of the drug through the membrane will govern the release kinetics.[184,207] Diffusion may occur through a reservoir in which a drug core is surrounded by a polymer film.[173,184] Reservoir devices without rate control delivery include membranes, capsules, microcapsules, liposomes and hollow fibers.[173] A hollow fiber system is a device consisting of a dialysis tube 5 mm long and 0.2 mm wide which is filled with a therapeutic agent and releases the drug by simple diffusion through reservoir walls. While the great advantage of reservoir systems is the ease with which they can be engineered to produce near zero order release kinetics, they also have several disadvantages.[184] They are marginally classified as sustained release devices because of the rapid release of chemotherapeutic agents. However, they also cause irritation of the pocket.[209]

3.1.2 | Matrix delivery systems

In matrix delivery systems the drug is homogeneously dispersed throughout a solid polymer matrix and release occurs via drug diffusion and/or matrix dissolution or erosion.[195] Those that release solely by diffusion use water-insoluble non-degradable polymers[210–212] whereas those that release by diffusion and matrix erosion or dissolution use soluble or biodegradable polymers in the matrix.[213–217] Several non-degradable polymers including poly (e-caprolactone), polyurethane, polypropylene, cellulose acetate propionate or copolymers such as poly ethyl vinyl acetate have been studied as materials for these drug delivery systems.[195] Other polymers utilized so far include chitosan, nylon, polycaprolactone, alginate and collagen.[206,218] From the standpoint of fabrication cost, the ease of accomplishing this distribution pattern represents a significant decrease in cost compared to reservoir systems. However because of the different way in which the drug is distributed, release characteristics are not generally zero order. During the past three decades numerous investigations documenting release kinetics and clinical effects have been conducted to evaluate the potential role of those controlled delivery systems in periodontal treatment.[219,220]

3.2 | Drug delivery devices in periodontal care

3.2.1 | Fibers

The term fiber is derived from the Latin word “Fibra” which means a fine thread. They are round and relatively long, of natural or a synthetic material and their length is significantly greater than their width. There are thread like and reservoir type drug delivery systems.[193] They can be hollow, with the drug loaded into the inner void volume or the more advanced ones are monolithic with the drug incorporated in the matrix. Newer technologies make use of nanofibers which have diameters in the nanometer range.[196]

Reservoir type hollow fibers

The first reservoir type prototype device using cellulose acetate dialysis tubing was introduced by Goodson et al.[181] to deliver solid tetracycline hydrochloride into the periodontal pocket. An appropriate length of tubing was administered by placement at the opening of the periodontal pocket and application of gentle pressure to insert it below the gingival margin. Hollow fibers rapidly release the drug by diffusion through the reservoir wall into the pocket. The drug-filled fibers provide drug therapy with less than 1/1000 of the amount of tetracycline that was required for systemic therapy.[181] Goodson et al.[181] explained that a single application of these fibers helped to inhibit periodontal microbiota by freeing the gingival sulcus effectively from spirochetes. However the hollow fiber released the tetracycline at a first order rate with 95% of the drug released in the first 2 h by diffusion but failed to provide controlled drug delivery for a prolonged time. Therefore a single application of these hollow fibers does not provide an effective drug concentration for long periods.[221]

In initial studies conducted using hollow fibers different drug solutions were incorporated into the reservoir devices for drug delivery to the periodontal pocket.[181,210,222,223] These studies rarely defined the device's drug delivery kinetics, instead attempted to demonstrate microbial and clinical outcomes. Clinical use of fibers containing chlorhexidine gluconate[222] and metronidazole[224] resulted in the reduction in the signs and symptoms of periodontal diseases. Compared with the less effective tetracycline delivery from hollow fibers, fibers containing 20% chlorhexidine exhibited a prompt and marked reduction in signs and symptoms of periodontal diseases.[222] The clinical improvements that resulted from use of the dialysis tubing delivery system may be attributed to the high initial concentration. Addy et al.[210] showed chlorhexidine to be released from reservoir fibers over 4 days in vitro and more than 95% of the drug release occurred in the first 24 h. On the other hand, placement of single tubing did not provide sufficient treatment to prevent pocket recolonization because the drug was placed at effective levels for 24 h. Although the hollow system served as a good drug holding device showing some clinical effects it was unable to sustain therapeutic levels of the drug for sufficient time to be clinically useful and they would therefore qualify only marginally as sustained release devices.[181,225] Release assays from these formulations indicated that the hollow fibers provide a good local reservoir for the drug but are poor rate limiting devices.[174]

Thread like fibers

As the hollow fibers have the property of rapid drug evacuation, second generation drug impregnated monolithic fibers were developed to retard drug release and increase the duration of the drug in the pocket.[174] Matrix type fibers were developed by incorporating the drug in molten polymers, with high temperature spinning followed by cooling.[212] Several polymers were used as matrices to construct these fibers.[226,227] Fibers were prepared by heat extrusion of tetracycline hydrochloride in poly(e-caprolactone) (PCL),

polyurethane, polypropylene, cellulose acetate propionate and ethyl vinyl acetate (EVA).[226,227] Rapid release was observed from polyethylene and polyurethane fibers with most of the drug released within 24 h. Polypropylene, PCL and cellulose acetate propionate fibers released only a small fraction of their drug load rapidly and could not provide an extended release profile.[212] EVA fibers produced a sustained in vitro release over 9 days and were proposed as a suitable carrier for tetracycline delivery in periodontal pocket disease. These initial studies were followed by others, notably those of Goodson et al.[212,221,223,225] which led to the development of the first USFDA and the European Union's regulatory agencies approved commercial tetracycline loaded fiber delivery system (Actisite, Alza Corporation).[212] Tonetti et al.[225] reported that EVA fibers containing 25% tetracycline hydrochloride providing gradual release over a 10-day period, in vitro, maintain a constant drug level above 600 μg/mL in the gingival crevicular fluid throughout 10 days showing the zero order release characteristics of EVA fibers.

In addition to extensive evaluation of drug delivery kinetics from EVA fibers this system has undergone numerous clinical trials to test its efficacy in the treatment of periodontal diseases. The clinical effectiveness of this system depends on whether it has been used as mono or adjunctive to periodontal therapy. Studies indicated that if used as a monotherapy without adjunctive SRP fibers were effective at reducing PD, gaining CAL[221,226,228,229] as well as reducing bacteria.[230,231] When monotherapy was compared to SRP, no additional clinical effect was found between the treatment methods.[221,226,228,229] When combined therapy was compared to SRP in periodontitis the clinical response was also similar[221,228,229] but enhanced SRP outcomes at non-responding sites.[227,232,233] On the other hand a 5-year controlled clinical trial reported no significant clinical difference after adjunctive tetracycline fiber therapy.[234]

This drug delivery technique is troublesome for both patient and clinician.[226] The process of fiber insertion is time consuming, requiring 7–10 min for application, and dislodging of the fibers during treatment has also been a considerable issue.[235] Patients experienced discomfort during placement and different degrees of gingival redness were observed after removal.[233] Moreover additional clinical time is required to apply these technologies subgingivally. The fibers were subsequently discontinued in 2003 (U.S. Food and Drug Administration).[236]

Periodontal Plus ABTM (Advanced Biotech Products) is a bioresorbable collagen fibril-based formulation with a dual mode of action containing the active agent tetracycline hydrochloride. Application of this fiber removes the need for a second appointment for fiber removal because it biodegrades within the pocket.[237] However a 12-month study conducted using the product reported insignificant clinical benefits.[238] The pharmaceutical technology for transforming fibers into intrapocket drug delivery systems has improved greatly since the introduction of hollow fibers in the 1970s. Today various modern pharmaceutical techniques are used to fabricate fibers or rather a pharmaceutical dosage form of nanofibers as a new means of intrapocket drug delivery.

3.2.2 | Strip/film/chips

Strips, films and chips are all polymer based thin bands of matrix systems designed to deliver the active therapeutic agents in a controlled and sustained fashion when precisely placed in the periodontal pocket. They are fabricated from a mixture of polymers, pharmaceutical additives and active drugs mixed in a hydrophobic or hydrophilic solvent. The methods of preparation include solvent casting and direct milling. Drug release from strip and films critically depends on the biodegradable property of the polymer. Biodegradable polymers release the drug by diffusion or matrix erosion, while non-degradable polymers release the drugs only by diffusion.[191,205] Strip and films have the advantages of being easily manipulated to fit the desired shape and size of the pocket and easy insertion with minimal discomfort to the patient.[215] Although strip, film and fibers share a similar range of polymers used in formulation, the key difference lies in their release rates based on dimensions and clinical application. Fibers have the advantage that they can be used in pockets present in an inaccessible region such as the distal surface of the last tooth in the dentition, whereas strip and films owing to their wider dimension, can be placed in broader pocket areas to achieve maximum clinical benefits.[239]

The pharmaceutical technology for nondegradable films is much simpler than for degradable ones. Thus, nondegradable formulations were the first to be introduced in literature. The first description of an intra-pocket non-biodegradable matrix delivery device introduced by Addy et al.[210] was of an acrylic (polyethyl methacrylate) (Orthoresin™) strip for controlled release of tetracycline, metronidazole and chlorhexidine over a 2–3 day period for the intra-pocket delivery. In clinical trials the tetracycline and metronidazole strips were found to be more effective at reducing the total anaerobic bacterial count than the chlorhexidine strips but returned to nearly baseline levels 4 weeks after treatment.[240–245] Physical properties of the acrylic strip were reported to be changed in the gingival crevicular fluid leading to the risk of leaving injurious acrylic material in the periodontal pocket where the surface of the strip was dissolved.[215] The other earliest non-degradable matrix for intra-pocket drug delivery was the ethylcellulose matrix film which was supplemented with chlorhexidine, metronidazole, tetracycline and minocycline.[211,246–249] Periodontal pockets treated with ethylcellulose film loaded with chlorhexidine exhibited a marked, albeit a short-term reduction in the relative numbers of spirochetes and motile rods which returned to pretreatment levels after 14 days.[211,249] The authors reported that metronidazole integrated into an ethylcellulose matrix could sustain therapeutic levels of metronidazole in vitro as well as in the gingival crevice fluid for 3 days.[248] Stabholz et al.[250] showed that the ethylcellulose strips with chlorhexidine led to prolonged clinical and microbiological improvements up to 11 weeks following therapy. They also reported that this formulation provided significantly better results than routine therapy in the maintenance of periodontal pockets over a 2-year period.[251] The in vitro release of niridazole from ethyl cellulose inserts was found to be steady

and sustained for over 7 days and also demonstrated a significant improvement in clinical indices and significant reduction in total bacterial count.[252]

It has been stated that the release of the therapeutic agent from these films is dependent on the solvent used, the presence of a plasticizer, the nature and concentration of the drug in the film and on the physical dimensions of the film.[253] The limitations of such delivery devices include the need for removal and replacement as they do not degrade. Therefore a strip that slowly erodes inside the pocket is an ideal method to obviate the disadvantages mentioned above.

Many biodegradable devices in the form of a strip or film have been fabricated and evaluated.[205] An array of degradable polymers are used in the synthesis of these systems such as polylactic acid, polyglycolic acid, poly caprolactone and poly hydroxyl butyric acid (PHBA).[169]

The earliest one, a resorbable hydoxypropyl cellulose based film containing chlorhexidine, tetracycline and doxycycline has been tested both in vitro and clinically.[216,254] In vitro studies demonstrated a rapid release of tetracycline and chlorhexidine from the film within 2 h with maximum dissolution occurring after 3 h. Significant clinical and microbiological advantages over the control group were described. Although this was a pioneering study in the development of biodegradable systems, the rapid degradation of the device and the short duration of drug exposure were distinct disadvantages.[216] Using a modification of this system by incorporating slowly soluble methacrylic acid copolymer particles into the hydoxypropylcellulose films impregnated with ofloxacin (PT-01), 70% of the drug was released from the device in the first 8 h in vitro and in vivo levels of ofloxacin were maintained for 7 days after treatment with the device. The authors suggested that the application of PT-01 as an adjunct in conventional periodontal therapy could provide beneficial effects.[255,256] Synthetic biodegradable PHBA and poly(lactide-*co*-glycolicacid) (PLGA) strips containing 25% tetracycline showed sustained release over four to 5 days with a significant burst effect at day 1,[244] whereas PLGA strips containing 25% tetracycline released therapeutic concentrations of the drug for 10 days.[257] So far no product has been marketed because of the non-biodegradation of the polymeric carriers and only temporary clinical improvements after treatment completion.

Some natural biodegradable collagen based polymers have been used for controlled release of antibacterial agents in the treatment of periodontitis.[217,258–263] A degradable delivery system using a 2% glutaraldehyde cross linked atelocollagen to deliver tetracycline has been developed.[263] Drug release kinetics, proof of therapeutic principle and clinical efficacy trials for a new controlled release device were investigated by the authors.[261–263] It has been demonstrated that tetracycline is released in therapeutic levels for 10 days after the insertion of the controlled release device. Clinical studies testing the efficacy of the system showed that one application of the tetracycline film resulted in a significant improvement in clinical parameters as well as microbiological parameters for 3–4 weeks following a single application.[261–263] The device was reported to dissolve in the pocket in about a week. A clinical study investigating another natural biodegradable system containing 5% metronidazole in collagen film gave a significant adjunctive effect on clinical parameters in the short term.[259] No information was provided about the nature of the matrix, the release kinetics of the device or its degradability. Another degradable natural sustained release device polymer based on gelatin obtained from fish (Byco protein) for the delivery of chlorhexidine diacetate or chlorhexidine hydrochloride has been described.[217] Based on this study a degradable controlled-release device has been developed and commercialized under the trademark Periochip® (Perio Products Ltd). It has the advantage over other biodegradable films in that it remains inside the pocket with no additional aids for retention because of the adhesive nature of the Periochip components.[264] Also, it is easily inserted into the pocket taking 1–2 min.[265] The system showed an initial burst release in the first 24 h followed by a constant slower drug release for a period of 7 days.[266] No traces of chlorhexidine were detected in the plasma or urine during that period.[266] Multicenter clinical trials were performed in Europe and the United States to test the clinical and microbiological effectiveness of the crosslinked protein film containing chlorhexidine.[191,251,267] It has been stated that there was a defined but limited clinical improvements in PD and CAL compared with control sites treated only by SRP.[191,267] No clinical or microbiological effect beyond conventional SRP over 9 months was observed by others.[268,269] An alternative form called Periocol®-CG (Eucare Pharmaceuticals Pvt. Ltd.) incorporates 2.5 mg chlorhexidine into a collagen membrane chip derived from fresh water fish.[270]

3.2.3 | Gels/semisolid forms

Biodegradable and injectable therapeutic agents in gel and semisolid forms are longstanding systems for administration of local antimicrobials into periodontal pockets. Gel-based devices offer some advantages over other device types such as its relatively practical production procedures, ease of application, dimensional stability, being moldable to fit to the 3D morphology of the periodontal pocket, being minimally invasive thus increasing patient compliance and having less irritative potential due to rapid eradication from the site via catabolic processes and fluid flow.[271–273] Concentration of an earlier slow release Minocycline HCl ointment (Periocline Sunstar; Dentomycin Atrix Laboratories) in the periodontal pocket has been demonstrated to decrease from 1266.5 to 11.2 μg/mL after only 24 h following administration.[274] Similarly a 50% carrier matrix of metronidazole containing gel was degraded from the application site in 6 h.[275] Although quick clearance of a highly concentrated drug lowers the potential side effects, retention and sustained release of the drug is expected to exert efficacy in antimicrobial, anti-inflammatory and wound healing. Therefore a controlled release (>24 h) that will maintain high concentrations for prolonged periods is more favorable[271,276,277] than a conventional slowly sustained release (<24 h). Therefore the goal of producing the most efficient controlled release in situ gel implant devices with improved bio-adhesiveness,

TABLE 5 Summary of investigated local drug (antibiotics and Chx) delivery systems and drugs in the semisolid & gel form.

Drug	Molecule incorporated in polymer matrix	Polymer	Commercial name	Commercially available European countries	Reference
Nitroimidazoles					
Metronidazole	15% Metronidazole	Chitosan			Akncbay et al. 2007[336]
	5% Metronidazole	Collagen Type I			Hitzig et al. 1997[337]
	5% Metronidazole	Hydroxyethyl cellulose/ carbopol + polycarbophil			Jones et al. 1997[338]
	25% Metronidazole benzoate	Poly-ε-caprolactone (PCL) + Carbopol 934P			Dabbhi and Sheth 2013[295]
	5% Metronidazole + 5% Doxycycline	Methylcellulose, hydroxyethylcellulose			Tiwari et al. 2010[171]
	Metronidazole (40% MET benzoate equivalent to 25% MET)	Glycerol monooleate + triglyceride (sesame oil)	Elyzol Dental Gel Dumex	Italy, UK	Norling et al. 1992[339] Lie et al. 1998[340] Kinane and Radvar 1999[341]
Satranidazole	0.25% Satranidazole	Sodium Carboxymethylcellulose			Bansal et al. 2009[292]
Tinidazole	5% Tinidazole	PLA + *N*-methyl-2-pyrrolidone + PEG 400 + glycerol			Quin et al. 2012[293]
Secnidazole	5% Secnidazole and/or 5% doxycycline	PLGA *N*-methyl-2-pyrrolidone			Gad et al. 2008[294]
Ornidazole	1% Ornidazole	Gellan gum + Lutrol F127			Dabhi et al. 2010[342]
	25% ornidazole + 10% doxycycline hyclate	Chitosan-vanillin crosslinked microspheres loaded in-situ gel			Yadav et al. 2018[296]
Tetracyclines					
Tetracycline	5% tetracycline & 5% tetracycline + 33% citric acid	TC gel: Poloxamer Mixture gel: Carbopol			Jeong et al. 1994[343]
	40% tetracycline paste	White petrolatum			Eckles et al. 1990[344] Unsal et al. 1994[345]
	3% Tetracycline ointment (Chlortetracycline hydrochloride)	Liquid paraffin, wool fat, petrolatum for 100 g	Aureomycine, Lederle Labs	Not a product for dental use originally	Lie et al. 1998[340]
	35% Tetracycline HCl	PLGA copolymer			Maze et al. 1996[257] Needleman et al. 1998[297]
	5% Tetracycline HCl	Hydroxyethyl cellulose + polyvinylpyrrolidone			Jones et al. 1996[346]
	3%–9% Tetracycline + serratiopeptidase	Pluronic F 127 + Aerosil 200			Maheshwari et al. 2006[347]

(Continues)

TABLE 5 (Continued)

Drug	Molecule incorporated in polymer matrix	Polymer	Commercial name	Commercially available European countries	Reference
Minocycline	2% Minocycline	Chitosan + ß-glycerophpsphate			Ruan et al. 2016[348]
	Minocycline hydrochloride 2%, 0.5 g in microcapsules gel	Hydroxyethyl cellulose + aminoalkyl-methacrylate + triacetine + glycerine	Periocline Sunstar	France, Ireland	van Steenberghe et al. 1993[349]
	Minocycline hydrochloride dihydrate 2% ointment		Dentomycin Atrix Laboratories	Poland, UK	Graca et al. 1997[350] Kinane and Radvar 1999[341]
	2% Minocycline (Periocline)	Liquid crystal (Propylene glycol + Phytantriol + water)			Yang et al. 2018[351]
Doxycycline	Doxycycline hyclate 10% (50 mg, equivalent to 42.5 mg doxycycline 8.5%)	Poly (D,L-lactide) + *N*-methyl 2-pyrrolidone	Atridox Block Drug; Atrix Laboratories Inc.	UK	Polson et al. 1997[299] Garrett et al. 1999[298] Ryder et al. 1999[300]
	14% doxycycline-hyclate (161.5 mg/g doxycline hyclate equivalent to 140 mg/g doxycycline)	Polyethylene glycolactid/glycolid copolymer	Ligosan, Ajjusan Heraeus Kulzer	Austria, Germany, Hungary, Italy, Poland, Spain (Ligosan), The Netherlands (Adjusan)	Eickholz et al. 2002[302] Ratka-Krueger et al. 2005[301]
	10% Doxycycline hyclate	Cholesterol, N-methyl-pyrrolidone + 10% benzyl benzoate			Phaechamud and Setthajindalert 2017[352]
Macrolides					
Azithromycin	0.5% Azithromycin	PLGA + N-methyl-2-pyrrolidone			Pradeep et al. 2013[353]
Clarithromycin	0.5% Clarithromycin	PLGA + N-methyl-2-pyrrolidone			Agarwal et al. 2012[354]
Lincosamides	1% Clindamycin hydrochloride	Carbopol + EDTA + TEA			Sauvetre et al. 1993[355]
	2% (10 mg/500 mg) Clindamycin hydrochloride	Not specified			Pejcic et al. 2015[356]
Quinolones	0.4% Moxifloxacin	Not specified			Flemmig et al. 2011[357]
	0.0125% Moxifloxacin	PLGA + Poloxamer 407			Beg et al. 2020[358]
Ureidopenicillins	Piperacilin sodium (100 mg) + Tazobactam sodium (12.5) mg	Amino- alkyl-methacrylate copolymer, ammonium methacrylate co- polymer, ethanol 95%	Gelcide MedTech Dental Periofilm T Asbacare Clinic® (Medirel AS)	Croatia, France, Italy, Lithuania, Poland, Switzerland	Sender-Janeczek et al. 2019[359] Lauenstein et al. 2013[303]
Bisbiguanides					
	1.5% chlorhexidine (0.5% chlorhexidine digluconate and 1.0% chlorhexidine dihydrochloride)	Chitosan + Xantan	Chlosite Ghimas	Austria, Georgia, Germany, Israel, Italy, The Netherlands, Poland, Russia, Spain	Paolantonio et al. 2009[304]
	0.1% CHX	Chitosan + beta-glycerophosphate			Ji et al. 2010[360]
	1.5% CHX + Ibuprofen	PLGA			Batool et al. 2019[361]

prolonged release time that reduces application frequency and thereby increases patient compliance, has been extensively studied. Prolonged action of the gel incorporated drug has been achieved by using oleogel, hydrogel, polymer, co-polymer based matrices such as glyceryl monooleate, caprolactone, PLGA, cellulose derivates and chitosan. Many gel formulations loaded with various concentrations of antibiotics belonging to the nitroimidazoles, tetracyclines, macrolides, lincosamides, quinolones, ureidopenicilins and antimicrobials including bisbiguanides have been developed, some of which have become commercially available in global and European markets (Table 5). Some other natural and synthetic products in gel or injectable form that have been tested for better management of periodontal diseases including extract of propolis, green tea cathechins, alendronate, simvastatin, taurolidine, probiotic bacteria species, quorum sensing inhibitors, silver nanoparticles, quercetin, hyaluronan, amino acid buffered sodium hypochlorite fall beyond of the scope of this chapter.[278–289]

A commercial gel containing 40% metronidazole benzoate equivalent to 25% metronidazole loaded in glyceryl monooleate and sesame oil triglyceride (Elyzol Dental Gel Dumex) is one of the earliest local delivery systems. The water free mixture transforms into a viscous liquid crystal state upon contact with gingival fluid. Although metronidazole could be detected up to 24–36 h after application,[290] half of the matrix component glyceryl monooleate was degraded in 6 h.[275] However 2 weekly applications of the metronidazole gel yielded a sustained beneficial transformation in microbiota up to 175 days.[291] Satranidazole,[292] tinidazole,[293] secnidazole[294] and ornidazole[295,296] are other nitroimidazole molecules which have been tested for efficacy as potential local delivery agents.

Although 35% tetracycline has been demonstrated to exceed MIC levels in GCF for 7 days (>100 μg/mL) and shown antimicrobial activity on some subgingival pathogens,[297] tetracycline derivatives doxycycline and minocycline alone or in combination with other antimicrobials have received greater attention as injectable gel/semisolid formulations. A flowable and erodible double syringe gel system containing 10% doxycycline (Atridox Block Drug; Atrix Laboratories Inc.) in poly (D,L-lactide) and *N*-methyl 2-pyrrolidone matrix (ATRIGEL Delivery System) the level of the antibiotic was found to be maximum (~1500 and ~2000 μg/mL) after 2 h following administration, remained above 1000 μg/mL through 18 h and well above the minimum inhibitory concentration for periodontal pathogens (≤6.0 μg/mL) for 7 days and showed more beneficial effects compared to SRP alone.[298–300] Similarly higher doses of adjunctive doxycycline (14% DOX) decreased counts of periodontopathogens for 3–6 months[301] and have provided more favorable PPD reduction than SRP (15% DOX)[302] (Ligosan/Adjusan, Heraeus Kulzer).

One of the latest LDD formulations for intrapocket delivery is a combination of penicillin and beta lactamase inhibitor (piperacillin and tazobactam, Periofilm T, Asbacare Clinic®, Medirel AS; Gelcide, IRES SAGL) that forms a barrier seal for retention of the gel. Administration of piperacillin/tazobactam is reported to reduce some periodontopthogens more efficiently than debridement alone but PPD and BOP reductions were found to be similar.[303] The other product is xanthan based chlorhexidine (Chlosite Ghimas). When combined with SRP, 65sXan-CHX gel produces more favorable PD reductions and CAL gains than SRP monotherapy in the short term.[304]

Although semisolid and gel forms are relatively earlier and less complicated in design than other delivery devices of interest, local intrapocket delivery of gels, even versions with slow release pharmacokinetics, may offer favorable improvements in PD reduction and CAL change both in the short and long term as was revealed by a recent meta-analysis.[305]

3.2.4 | Microparticulate systems

Microparticles also known as microspheres are solid spherical polymeric structures with a diameter range of 1–1000 μm containing a drug dispersed throughout the polymeric matrix.[197,306] They are designed to contain active therapeutic agents that are uniformly distributed throughout the polymer matrix to protect drugs from the external environment and eliminate incompatibility.[307] Microparticles have many advantages like shielding unstable drugs before and after administration, providing sustained and controlled drug release at the target site, improving patient compliance, enhancing bioavailability and decreasing frequency and intensity of adverse effects.[308]

Many nonbiodegradable and biodegradable materials are utilized for microencapsulation including polymers of natural origin, modified natural substances and synthetic polymers.[197] The type of polymer used which determines the time and the release rate of therapeutic agents in the targeted site is of importance as it affects the properties of microspheres such as physiochemical and mechanical properties, mechanism, and rate of biodegradation and toxicity.[197] The biodegradable synthetic polymers include polyesters, polyanhydrides, and natural polymers like chitosan, pectin, hyaluronic acid, and alginic acid.[309] Water soluble polymers like gelatin, starch and insoluble polymers like ethyl cellulose, polyethylene are also used for microencapsulation.[310] Various methods including solvent evaporation, coacervation, electrospraying, phase separation and spray drying were used in the formulation of microparticles.[215] Microparticles can be formulated as a chip or dental paste or can be injected directly into the pocket.[311]

Several clinical studies have demonstrated the use of drug loaded microspheres and microcapsules for the delivery of encapsulated antibacterial agents in treating periodontal diseases. Microcapsules are dissolution controlled polymeric reservoir devices which may deliver their contents with a prolonged release profile in the salivary or crevicular fluid.[193] Microcapsules prepared from lactic acid and or glycolic acid copolymers have been proposed for delivery of tetracycline and minocycline.[213,312] Tetracycline containing microcapsules in Pluronic F127 were reported to form a gel at body temperature to hold the microcapsules in the periodontal pocket for the duration of the treatment.[213] Minocycline microcapsules when administered in a dry state to the periodontal pockets of beagle dogs showed an effective minocycline concentration which

TABLE 6 Relative effects on PD and CAL reduction from systematic reviews/meta-analyses concerning SRP plus local antimicrobial delivery compared to SRP alone or SRP plus placebo vehicle (non-significant [NS] clinical data are not shown for the individual drug subgroup analyses). WMD = weighted mean difference

Reference	PD reduction (mm)	CAL reduction (mm)	BOP reduction	PI reduction
Hanes and Purvis 2003[362] 28 RCTs, 2 CCTs, 2 cohorts	WMD: 0.34	WMD: 0.06		
	CHX chip: 0.55 (4 studies)	CHX chip: 0.27 (4 studies)		
	DOX gel: 0.36 (2 studies)	DOX gel: 0.23 (2 studies)		
	MET gel: 0.02 (2 studies)	MET gel: 0.04 (1 study)		
	MINO gel: 0.31 (4 studies)	MINO gel: 0.13 (1 study)		
	MINO micro: 0.54 (3 studies)	MINO micro: −1.3 (1 study)		
	TET fiber: 0.1 (4 studies)	TET fiber: −0.13 (4 studies)		
Bonito et al. 2005[363] 50 RCTs Based on antibiotic/antimicrobial molecule, not the specific delivery system	WMD range: 0.25–0.50	WMD range: 0.10–0.50		
	CHX: 0.24 (2 studies subgingival irrigation, 1 study 1% gel, 1 study 1% gel with the full-mouth disinfection approach)	CHX: 0.16 (7 studies)		
	MET: 0.32 (6 studies 25% gel, 1 study strip)	MET: 0.12 (6 studies 25% gel, 1 study strip)		
	MINO: 0.49 (3 studies microsphere, 2 studies gel, 1 study ointment)	MINO: 0.46 (5 studies)		
	TET: 0.47 (1 study TET irrigation, 1 study TET 3% ointment, 1 study, TET & TET + citric acid paste, 1 study 40% TET paste, 2 studies TET fiber)	TET: 0.24 (In addition to studies in "PD reduction" column 1 study TET fiber, 1 study single & multiple applications of TET strip, 1 study TET fiber in furcations)		
Matesanz et al. 2013[364] 52 RCTs	WMD: 0.41	WMD: 0.31		
	CHX chip: 0.33 (9 studies)	CHX chip: 0.22 (10 studies)		CHX chip: −0.15 (3 studies)
	CHX varnish: 0.41 (3 studies)	CHX varnish: 0.03 (2 studies)	CHX varnish: 4.84 (3 studies)	
		CHX-Xan gel: 0.89 (2 studies)		
	DOX: 0.57 (5 studies)	DOX: 0.22 (7 studies)		
	MET: 0.16 (5 studies)	MET: −0.01 (5 studies)	MET: 4.48 (3 studies)	
	MINO: 0.47 (8 studies)	MINO: 0.19 (7 studies)		MINO: −0.24 (3 studies)
	TET fiber: 0.73 (5 studies)	TET fiber: 0.33 (5 studies)	TET fiber: 24.95 (2 studies)	TET fiber: 0.15 (3 studies)
		TET strip: 0.46 (2 studies)		
Smiley et al. 2015[365] 72 RCTs		WMD: 0.35 (Addition to local delivery systems SDD, sys abs, lasers & PDT were also included)		
		CHX chip: 0.40 (6 studies)		
		DOX gel: 0.64 (3 studies)		
		MINO micro: 0.24 (5 studies)		

TABLE 6 (Continued)

Reference	PD reduction (mm)	CAL reduction (mm)	BOP reduction	PI reduction
John et al. 2017[366] Network Meta Analysis 61 RCTs		WMD: 0.32 (Addition to local delivery systems SDD, sys abs, lasers & PDT were also included)		
		CHX chip: 0.40 (6 studies)		
		DOX gel: 0.64 (3 studies)		
		MINO micro: 0.24 (5 studies)		
Wang et al. 2020[367] Network Meta Analysis 22 RCTs	<3 months	<3 months		
	CHX chip: 0.67	CHX chip: 0.48		
	TET fiber: 0.57	TET fiber: 0.30		
	4–6 months	4–6 months		
	CHX chip: 0.65	CHX chip: 0.61		
		DOX gel: 0.70		
	TET fiber: 0.64			
	>6 months	>6 months		
	None of the interventions were significant	None of the interventions were significant		
Tan et al. 2020[186] Network Meta Analysis 45 RCTs	Split mouth design	Split mouth design		
	CHX chip: 0.30	CHX chip: 0.10		
	CHX-Xan: 0.60	CHX-Xan: −0.56		
	DOX gel: 0.15	DOX gel: 0.14		
	MET gel: 0.21	MET gel: 0.50		
	MINO gel: 0.97	MINO gel: 0.52		
	MINO micro: 0.93	MINO micro: 0.65		
	Parallel design	Parallel design		
	CHX chip: 0.02	CHX chip: 0.50		
	CHX-Xan: 0.31	CHX-Xan: 0.16		
	DOX gel: 0.90	DOX gel: 0.84		
	MINO gel: 0.67	MINO gel: 0.69		
	MINO micro: 0.26	MINO micro: 0.13		
	TET fiber: −0.14	TET fiber: −0.07		
Herrera et al. 2020[305] 50 RCTs	WMD: 0.36 (6–9 m) (38 studies)	WMD: 0.26 (6–9 m) (10 studies)		
	CHX chip: 0.23 (9 studies)		CHX chip: −7	
	CHX-Xan: 0.49 (2 studies)	CHX-Xan: 0.84 (1 study)	CHX-Xan: 22	
	DOX Gel 10%: 0.80 (2 studies)	DOX Gel 10%: 0.64 (1 study)	DOX Gel 10%: 12.5	
	DOX Gel 14%: 0.52 (3 studies)	DOX Gel 14%: 0.41 (3 studies)		
	MINO micro: 0.28 (6 studies)	MINO micro: 0.52 (4 studies)		
	TET fiber: 0.73 (7 studies)			
		TET strip (multi): 0.48 (1 study)		
	WMD (12–60 m): 0.19	WMD (12–60 m): NS		

was maintained for nearly 2 weeks.[312] Biodegradable microparticles containing poly(a-hydroxyacids) such as poly(lactide) (PLA) or PLGA have been designed for the site specific delivery of tetracycline and histatins.[313,314] The in vitro drug release profile showed drug and polymer stability for up to 11 days. The formulation also achieved a significant improvement in clinical and microbiological parameters up to 3 months compared to commercial doxycycline gel.[315] Doxycycline loaded PLGA microspheres showed a sustained release of the drug in the periodontal pocket for 20 days.[202] It has been demonstrated that doxycycline hyclate-loaded in situ forming microparticles exhibited a sustainable drug release for 47 days with Fickian diffusion effectively inhibited *P. gingivalis*, *S. mutans*

and *Staphylococcus aureus*.[316] In another study doxycycline loaded microspheres showed sustained drug release behavior for up to 21 days and effective inhibition of *P. gingivalis* and *Fusobacterium nucleatum*.[317] Although these in vitro studies seem promising, as the drugs are slowly released in a controlled manner over a period of 2 weeks to 1 month, some questions about the retention of such formulations in the periodontal pocket need clarification.

The PGLA-based minocycline hydrochloride loaded 1 mg/unit dose cartridge microsphere was designed for sustained subgingival delivery in the periodontal pocket and granted marketing approval by US FDA Arestin®.[318] Clinical data indicated that minocycline concentrations are sufficient for up to 14 days and are effective in inhibiting bacterial activity.[319] The advantages based on the clinical data analysis including controlled release, increased bioavailability and bactericidal activity suggest that the microsphere has potential as a drug delivery system in periodontal care. Gingival crevicular fluid hydrolyzes the polymer and releases minocycline for a period of 14 days or longer before resorbing completely.[214] The result of a multi-center clinical trial of minocycline microspheres exhibited significantly greater probing depth reductions as compared to control subjects treated with mechanical therapy alone.[320] Over a 2-week period, the minocycline diffused from the microspheres during hydrolysis. Other studies failed to demonstrate any improvement over mechanical debridement in the long term despite repeated subgingival minocycline treatment over 24 months.[321,322]

3.2.5 | Nanoparticulate systems

Thanks to the most recent promising advances in nanotechnology, synthesis of biodegradable carriers of nanometric size and controlled nanostructures, modern drug delivery systems are gaining extensive attention in the biomedical field of periodontology.[323–326] They are highly dispersible in an aqueous medium, have a controlled release rate and are stable. Nanosizing the drug can lead to a dramatic increase in their absorption and bioavailability. Uniform drug distribution over a long period of time results in a reduction in dosage frequency.[326] Nanoparticulate systems are biocompatible, mostly bio-degradable and can easily be modified or combined for drug loading.[327] Because of their small size with a dimension of less than 100 nm they can penetrate into the regions that may be inaccessible to other delivery systems.[326] While only the 1 nm-100 nm size of materials, was defined in the earliest definitions, nanotechnology is currently being exploited to promote and control biological interactions as nanoscale materials (1–100 nm) are ubiquitous.[325] Nanotechnological drug delivery approaches are highly promising for what is expected from an ideal drug delivery system.[187,328] Some of these approaches have demonstrated satisfactory outcomes toward minimizing undesirable side effects for various active agents while maximizing therapeutic activity. It provides an opportunity for therapeutic molecules to be capsulated and loaded in carriers, such as nanoparticles or scaffolds to allow targeted, sustained and controlled release to the intended location.[323]

The nanoparticulate system provides several advantages over microspheres, microparticles and emulsion based delivery systems. This novel drug delivery system can be applied in a matrix of traditional local applications such as membranes, fibers, or gels. Among the various promising nanotechnology-based approaches, specific examples of nanocarriers or nanomaterials such as liposomes, lipid and polymeric nanoparticles, nanocrystals, dendrimers and nanofibers are under development for use in the treatment of periodontal diseases.[323,324,326,329] Three types of nanoparticles used for drug delivery are defined; one is monolithic nanoparticles also termed nanospheres in which the loaded active drug is adsorbed, dissolved, or dispersed throughout the particle matrix, second is nanocapsules where the active drug is trapped, dissolved, or dispersed in a hydrophilic or lipophilic medium surrounded by a shell-like wall, and thirdly nanoparticles in which the drug is the main component of the pharmaceutical formulation.[196] They are usually manufactured from copolymers such as PLGA, poly(D,L-lactide) (PDLLA), poly(ethylene glycol) (PEG) and other biopolymers like lipid, chitosan, pectin and alginate.[194] The use of nanotechnology such as nanoparticles for intrapocket drug delivery has recently garnered substantial scientific and clinical attention as a potential treatment regime for periodontal diseases. However, research into this type of delivery system, in the pharmaceutical form of a sustained-release drug delivery system for the treatment of periodontal diseases, is still in its infancy.

4 | GENERAL RECOMMENDATIONS BASED ON CURRENT CLINICAL GUIDELINES

The European Federation of Periodontology (EFP) has developed and recently published an evidence based guideline[18] (*The Treatment of Stage I–III Periodontitis – The EFP S3-level Clinical Practice Guideline*) to guide clinicians to choose the best option for treating periodontitis according to the new classification of periodontal and peri-implant diseases and conditions with the guidance based upon updated evidence of the highest level. Recommendations are based mainly on the efforts of 90 experts who comprehensively assessed 15 systematic reviews on various periodontal therapy alternatives, along with their applicability, harm benefit, cost benefit and other considerations in the 16th European Workshop on Periodontology held in 2019. Each recommendation debated was specified with an individual grade of recommendations were based upon consensus agreement: [*Grade A: strong recommendation we recommend* (↑↑)/*recommend not to* (↓↓); *Grade B: recommendation, we suggest to* (↑)/*we suggest not to* (↓); *Grade O: open recommendation– may be considered* (←→)].

Considering *topical supragingival application of antiseptics*, it has been proposed that adjunctive antiseptics may be considered during Step 2 (chlorhexidine rinses) and supportive periodontal care (chlorhexidine, triclosan copolymer and stannous fluoride-sodium hexametaphosphate as dentifrices or chlorhexidine, essential oils and cetylpyridinium chloride as mouth rinses) in specific cases as part of personalized treatment approaches.

The *local subgingival application of antiseptics* also called subgingival irrigation has some merit as a professional application and in combination with SRP, but is not recommended for inclusion in a patient's daily home care routine. Self-administered direct cleaning of pockets is either not possible or extremely difficult to perform and is not a realistic approach.

The comparative clinical effects on PD and CAL reduction using SRP plus local antimicrobial delivery as compared to SRP alone or SRP plus a placebo vehicle according to systematic reviews and meta analyses are summarized in Table 6. Some *locally administered antibiotics* may provide beneficial outcomes over non-surgical periodontal monotherapy in patients with periodontitis. However the effectiveness of locally administered sustained release antibiotics as adjuncts to subgingival instrumentation in patients with periodontitis is still subject to considerations concerning heterogeneity, risk of bias, unclear cost benefit and harm benefit issues, and limited availability. In addition, there are concerns regarding the clinical significance of the beneficial effects, the difficulty in defining an evidence based application protocol and limited information on the clinical characteristics of the specific patient group that would benefit the most.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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