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Review article

Local delivery of antimicrobial agents for the treatment of periodontal diseases

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Abstract

Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by groups of specific microorganisms. Aggressive forms of periodontitis can be localized or generalized. The concept that localized problem sites may be treated by local drug delivery appears attractive as the antimicrobial agent is delivered within periodontal pockets and the therapy is targeted on specific pathogenic microorganisms. Local delivery of antimicrobial agents using controlled release systems should be considered as adjunctive to mechanical debridement for the treatment of localized forms of periodontal destruction. This article reviews various types of delivery systems evaluated in practical periodontal therapy. Despite the large number of studies showing an enhanced effectiveness of local antibiotherapy, there are insufficient comparative data to support any of the local delivery system.

Keywords: Controlled drug delivery; Local antibiotherapy; Periodontal disease

1. Introduction

Periodontal diseases is a general term which encompasses several pathological conditions affecting the tooth supporting structures. Periodontal diseases include conditions such as chronic periodontitis, aggressive periodontitis, systemic disease-associated periodontitis and necrotizing periodontitis [1]. These conditions are characterized by a destruction of the periodontal ligament, a resorbtion of the alveolar bone and the migration of the junctional epithelium along the tooth surface (Fig. 1). The clinical signs of periodontitis are changes in the morphology of gingival tissues, bleeding upon probing as well as periodontal pocket formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria [2]. The microorganisms colonizing the subgingival area represent the principal etiological factor in the development of the inflammation and tissue destruction. Healthy periodontium is associated with a simple bacterial population which predominantly consists of non-mobile coccoid cells and rods. Subsequently, there is a shift in the microbial composition as the biofilm matures. The microflora found in periodontitis is complex and composed mainly of Gram negative anaerobic bacteria [3]. Moreover, studies have shown that the various clinical forms of periodontitis are associated with different microbiota [4] (Table 1). The exact mechanisms of tissue destruction are not completely elucidated. Suspected periodontal pathogens have been shown to produce a large number of biological molecules that may act directly on host tissue and destroy its integrity. On the other hand, there is evidence suggesting that the multitude of inflammatory and immune mediators produced by the host may cause tissue injury.

The aim of current periodontal therapy is to remove the bacterial deposits from the tooth surface and to shift the pathogenic microbiota to one compatible with periodontal health. Therapeutic approaches include mechanical scaling and root planing and, in some cases, surgery. As a result of treatment, there is a decrease of gingival inflammation as well as clinical probing depth [5]. Unfortunately, in some instances, the complex anatomy of the root and the contours of the lesion may hamper the treatment and prevent sufficient reduction of the bacterial load to make the tooth surface biologically acceptable. In addition, control of supragingival plaque is essential in order to prevent recolonization of the subgingival area by periodontal pathogens [6]. Indeed, several clinical studies have clearly indicated

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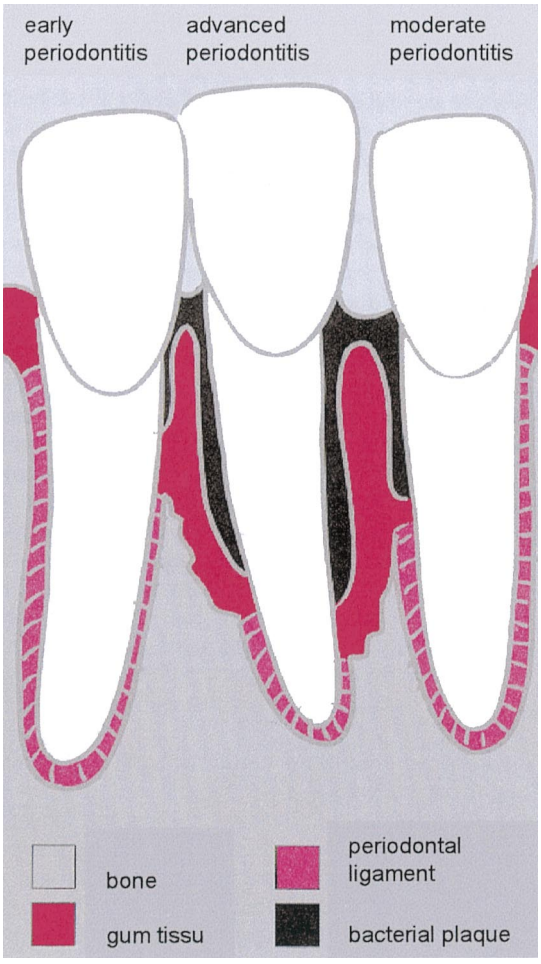

Fig. 1. Bacteria in subgingival plaque have caused a periodontal pocket to develop, inflaming surrounding tissue and causing loss of alveolar bone (source: Swiss Society of Periodontology).

that scaling and root planing, in combination with optimal oral hygiene, results in an alteration of the subgingival plaque which is sufficient to stop periodontal destruction in most cases [7]. It also has been shown that patients who fail to achieve acceptable plaque control during or after subgingival treatment frequently suffer from recurrent periodontitis [8–10]. Thus, oral hygiene is of the utmost importance for the clinical outcome of non-surgical as well as surgical treatment. However, severe or aggressive forms of periodontitis in young subjects often cannot be arrested by mechanical treatment alone. Furthermore, there are some patients or sites where even repeated treatment fails to stop the disease. These are referred to as refractory subjects or non-responding sites [11]. This could be related to the persistence of pathogens in the pocket after treatment or to the production by the bacteria of specific virulence factors interfering with the host defense (e.g. leukotoxin production, encapsulation, etc.). It also could be due to the recolonization of treated sites from bacterial reservoirs such as dentinal tubules and soft tissues [12,13]. In this context, it is evident that antimicrobial agents are of great interest and may be valuable as adjuncts to mechanical therapy [14].

Systemically applied antimicrobials have been advocated for the treatment of severe forms of periodontitis. However, in the early 1970s, concern emerged with respect to systemic antibiotherapy for chronic infections such as periodontal disease. Indeed, side effects including hypersensitivity, gastrointestinal intolerance and the development of bacterial resistance have been described [15,16]. Some studies also reported poor results due to the fact that the active product could not achieve an adequate concentration at the site of action and/or due to the inability of the active product to be retained locally for a sufficient period of time [17]. These drawbacks would be markedly reduced if antimicrobial agents applied locally could be used, although unwanted effects such as gastrointestinal disturbances and development of antibiotic resistance cannot be totally ruled out. The local tissue concentration of a drug can be enhanced by incorporating the active agent into controlled release delivery systems to be placed directly in the periodontal pocket. Such systems may have applications where systemic drugs are currently used, for instance localized juvenile periodontitis, refractory periodontitis and periodontitis with secondary systemic involvement, e.g. HIV periodontitis. Sustained local delivery systems might also be recommended for sites considered as difficult to instrument because of depth or anatomical complexity, for example in the case of furcation defects [18,19]. More controversial

Table 1
Microbial species associated with various clinical forms of periodontitis (data from Refs. [3,4,12]: Haffajee and Socransky, 1994; Moore and Moore, 1994; Van Winkelhoff and Winkel, 1996)[a]

Species	Juvenile periodontitis	Early onset periodontitis	Adult periodontitis	Refractory periodontitis
Actinobacillus actinomycetemcomitans	+++	++	++	+ to ++
Porphyromonas gingivalis	±	+++	+++	++
Prevotella intermedia	++	+++	+++	+++
Fusobacterium nucleatum	+	++	+++	++
Eikenella corrodens			+++	
Bacteroides forsythus	±	++	+++	++

[a] ±, occasionally isolated; +, <10% of the patients positive; ++, <50% of the patients positive; +++, >50% of the patients positive.

would be the replacement of root planing by controlled release devices. However, studies suggest that these systems, used as adjuncts to scaling and root planing, give a slight advantage over mechanical treatment alone, although the clinical difference has often been insignificant [20–27]. This may be because scaling and root planing alone is usually quite effective in producing clinical and statistically significant improvements. On the other hand, few studies have evaluated the effects of local drug delivery systems on sites that responded poorly or showed recurrence after scaling and root planing [10]. If improvements are maintained for a long-term period, then such systems would be an interesting tool in the management of localized periodontal lesions. For most studies dealing with local delivery systems, the treatments did not result in any serious adverse effects and were well tolerated by the patients.

2. Drug delivery devices

There are two possible approaches to improve the drug action: (i) sustained and controlled drug release to reduce or eliminate side effects by improving the therapeutic index; (ii) site-specific drug delivery to minimize systemic effects. These two strategies have been explored by the association of drugs with different vehicles, either naturals or synthetics. However, most of these systems failed to realize their potential in clinical phase studies. In this respect, it is critical not to under-estimate problems such as weak therapeutic activity resulting from a limited accessibility to the tissue to be treated or toxicity and/or immunogenicity of the delivery system [28]. Synthetic polymers have proved to be extremely interesting because they can be tailor-made to meet pharmacological or biological requirements.

Drug delivery systems can be classified according to the mechanism controlling drug release. We distinguish three categories: (i) 'solvent controlled' matrix systems based on macromolecular matrix permeability to small molecules after matrix swelling into hydrated medium; (ii) 'reservoir systems' controlled by drug diffusion across a polymeric membrane; (iii) 'chemically controlled systems' where the rate of drug release is controlled by the rate and extent of degradation of chemical bonds and the erosion of the polymeric matrix. For all these systems, the basic polymer can be of natural origin such as proteins [29] or collagen [30], semi-synthetic such as cellulose derivatives [31,32] or synthetic, all of which must preferably degrade during use. Natural polymers have been considered as biodegradable carriers [33]. However, most of them have disadvantages inherent to their structure, including limited half-life, complexity of composition and immunogenicity due to the polymer itself or to its degradation by-products.

Many polymer based systems for antibiotic delivery in the treatment of periodontal diseases have been studied and evaluated in vitro and/or in vivo (Table 2). Unfortunately, the majority of the studies provide little indication of the effect of the preparation on the progression of periodontitis. In addition, few clinical data were reported and therefore no association between changes in the flora and changes in disease patterns could be established. Some of these systems are not resorbable, while most are biodegradable. Non-biodegradable systems have to be removed after complete drug release, which may cause irritation and inflammation of the treated site. Conversely, a biodegradable sustained-release drug delivery system which can be placed into the periodontal pocket and maintain therapeutic concentrations for prolonged periods of time would be advantageous. Indeed, in addition to improving compliance over systemic antibiotics, biodegradable devices are cost effective as they will not require a second visit to the periodontist for removal.

To be useful for periodontal therapy, it is desirable to have a bioerodible drug delivery system that can maintain an effective drug release rate in the periodontal pocket while simultaneously eroding throughout the duration of treatment up to several days.

2.1. Antimicrobial choice

The choice of the antimicrobial agents in periodontal diseases must be based on the bacterial etiology of the infection [10]. Several antibiotics have been tested for their clinical and microbiological efficacy in periodontal diseases. It can be noted from Table 1 that only a limited number of antimicrobial agents have been used so far in formulations of delivery systems. Basically, we distinguish antiseptic agents such as chlorhexidine and sanguinarium from antibiotic agents which can be differentiated by their mode of action and their spectrum of susceptible microorganisms. Some antimicrobial agents have been selected because of their substantivity which refers to the property of some medications that have an intrinsic ability to bind to the soft and/or hard tissue walls of the pocket [34].

2.1.1. Chlorhexidine

The use of chlorhexidine as an antifungal and antibacterial agent in dentistry is well documented. Its major application has been for the control of dental plaque. However, a number of studies have indicated that chlorhexidine is also effective in periodontitis [35]. Chlorhexidine was primarily used in mouth-rinses and was recommended in the hygiene phase of treatment as an adjunct to tooth-brushing. Most attention, however, has been focused on the use of chlorhexidine during the operative and immediate post-operative phases of non-surgical and surgical periodontal treatment [36]. Chlorhexidine's potential effects at these times are: (i) a surface bacteriostatic action; (ii) improved wound healing and patient preference to dressings in the immediate-post-surgical phase; (iii) optimum plaque control immediately post-treatment when discomfort may compromise tooth-cleaning. Further studies have shown that slow release

Table 2
Summary of some investigated local controlled delivery systems for antimicrobial agents (commercial name in bold)[a,b]

Type of device, product name (company)	Polymer	Drug	Drug loading (%)	Degradability of the carrier	Reference
Microtubules	Diacetylenic phosphatidyl cholines	Tetracycline	5	No	[98] Price and Patchan, 1991
Monolythic fiber, **Actisite®** (**Alza Corporation**)	Ethylene vinyl acetate copolymer	Tetracycline HCl	25	No	[57] Tonetti et al., 1990; [73] Goodson et al., 1983; [74] Michalowicz et al., 1995; [76] Drisko et al., 1995
Strip	PHBA	Tetracycline HCl	50	Yes	[80] Collins et al., 1989
Strip	PHBA	Metronidazole	25	Yes	[79] Deasy et al., 1989
Strip	PHEMA	Doxycycline	30	No	[78] Larsen, 1990
Strip	PMA + HPC	Ofloxacin	10	No	[71] Kimura et al., 1991
Film	Cross-linked collagen	Tetracycline	50	Yes	[30] Minabe et al., 1989
Film	Bycoprotein + glycerol	Chlorhexidine diacetate, chlorhexidine HCl	10–15	Yes	[29] Steinberg et al., 1990
Film	Eudragit	Clindamycin	5	No	[66] Higashi et al., 1991
Film	PLGA	Tetracycline HCl	5/25	Yes	[81] Webber and Mathiowitz, 1997; [82] Agarwal et al., 1993
Film	CAP + PEO-PPO	Metronidazole	10	Yes	[99] Gates et al., 1994
Film	EC	Metronidazole/ chlorhexidine	20/20	Yes	[31] Loesche et al., 1996
Film	POE	Metronidazole	5–10	Yes	[83] Vasavada and Junnarkar, 1997
Insert, **Periochip®** (**Perio Products Ltd**)	Cross-linked hydrolyzed gelatin + glycerin	Chlorhexidine gluconate	33	Yes	[38] Goffin, 1998
Microspheres	PLGA	Minocycline	25	Yes	[86] Jones et al., 1994
Microspheres	PLGA	Histatin peptides	0.125	Yes	[85] Jeyanthi et al., 1997
Microspheres	PLGA, PLA	Tetracycline	20	Yes	[84] Esposito et al., 1997
Mucoadhesive gel	Carbopol	Clindamycin	1	No	[67] Sauvetre et al., 1993
Mucoadhesive gel	HEC + PVP	Tetracycline	5	No	[88] Jones et al., 1996
Mucoadhesive gel	HEC + carbopol + polycarbophil	Metronidazole	5	No	[87] Jones et al., 1997
Mucoadhesive gel	HPMC	Histatin peptides	0.125	Yes	[32] Paquette et al., 1997
Lipid-like gel, **Elyzol®** (**Dumex-Alpharma**)	Glycerol monooleate + sesame oil	Metronidazole	25	No	[10] Noyan et al., 1997; [36] Addy and Renton-Harper, 1996; [94] Radvar et al., 1996
Lipid-like gel	PEO-PPO + glycerol monooleate	Tetracycline	5	No	[90] Esposito et al., 1996
Lipid-like gel, **Dentomycin®** (**Lederle Laboratories**), **Periocline®** (**Sunstar Co. Ltd**)	HEC + aminoalkyl methacrylate copolymer + triacetine + magnesium chloride + glycerin	Minocycline	2	No	[91] Nakagawa et al., 1991; [92] Hayashi et al., 1998; [93] Graça et al., 1997; [94] Radvar et al., 1996
Liquid system, **Atrigel®**, **Atridox™** (**Atrix Laboratories**)	PLA + NMP	Doxycycline hyclate	10	Yes	[95] Polson et al., 1996; [96] Polson et al., 1997; [97] Yewey et al., 1997
Liquid system, **Atrigel®**	PLA + NMP	Sanguinarium	5	Yes	[51] Polson et al., 1997; [52] Polson et al., 1996
Injectable semi-solid system	POE + $Mg(OH)_2$	Tetracycline HCl	10	Yes	[100] Roskos et al., 1995

[a] PHBA, poly(hydroxybutyric acid); PHEMA, poly(2-hydroxyethyl)-methacrylate; PMA, poly(methacrylic acid); HPC, hydroxypropyl cellulose; PLGA, poly(lactide-co-glycolide) 50/50; CAP, cellulose acetate phthalate; PEO-PPO, poly(ethyleneoxyde-co-propyleneoxyde) (PluronicL101); EC, ethyl cellulose; POE, poly(ortho ester); PLA, poly(lactide); HEC, hydroxyethyl cellulose; PVP, polyvinylpyrrolidone; HPMC, hydroxypropylmethyl cellulose; NMP, *N*-methyl-2-pyrrolidone.
[b] Commercial names in bold.

devices in the mouth are even more effective, especially for the treatment of periodontal pockets [18,29].

Chlorhexidine appears particularly effective in reducing plaque and gingivitis. Its mechanism of action relates to reduction in pellicle formation, alteration of bacterial adherence to teeth, and an alteration of bacterial cell walls, causing lysis [37]. Its antibacterial action is due to an increase of the cellular membrane permeability, followed by the coagulation of intracellular cytoplasmic macromolecules [38].

Because chlorhexidine is highly cationic, it exhibits high substantivity. Its chemical structure allows it to remain in the oral cavity for a prolonged period after a single rinse and

thereby function in a slow release type manner [39]. The long-term efficacy of chlorhexidine on the periodontal pocket flora is dependent on the duration of exposure. Intra-crevicular irrigation of the periodontal pocket with chlorhexidine has only a short-lived effect on the pocket flora. The sustained release of chlorhexidine for 3 days showed longer and significant changes for up to 14 days while 9 days of sustained exposure to chlorhexidine resulted in significant changes lasting for as long as 11 weeks [40].

Despite these attributes, chlorhexidine presents some disadvantages, including staining of teeth, taste disturbances and an increase in calculus accumulation. In general, chlorhexidine and other topical agents fail to penetrate deep into periodontal pockets, hence their effects are limited to supragingival areas.

2.1.2. Sanguinarine

Sanguinarine, a benzophenanthridine alkaloid with a wide-spectrum antiseptic activity in vitro, was obtained from the bloodroot plant (*Sanguinaria canadensis*) [41,42]. Short-term studies have shown some plaque and gingivitis reduction [43–45]. However, the results of long-term studies are conflicting: some showed no reduction in plaque or gingivitis [46,47], whereas others demonstrated a significant reduction when patients used both mouth-rinse and dentifrice forms [48,49]. The proposed mechanism of action is an alteration of the bacterial wall, so that aggregation and attachment are reduced. The product may be cationic and the degree of substantivity is unclear. Adverse effects include a burning sensation of the mouth.

Sanguinarine appears to have less antimicrobial activity than drugs with known clinical effectiveness. Its MIC against periodontal pathogens has been reported to range from 1 to 32 μg/ml compared to 0.06–32 μg/ml for tetracyclines. Local application of sanguinarine via a controlled release system showed low clinical efficacy [50,51]. The reason for this may be due to its conversion to the pseudobase form. This conversion has been shown to occur above pH 6.0 leading to increased insolubility and resulting in reduced bioavailability. With the pH of gingival crevicular fluid (GCF) in a periodontal pocket being in the range of 7.5–7.9, it is the likely cause of the sanguinarine conversion to its less bioavailable form [52].

2.1.3. Histatins

The histatins are a group of small, cationic histidine-rich peptides secreted by human parotid and submandibular salivary glands. These endogenous peptides have been shown to bind to hydroxyapatite, suggesting a role in the formation of the acquired enamel pellicle. The histatins play a major role in protecting the host oral cavity from etiologic pathogens. In particular, the histatins are antifungal and also demonstrate bactericidal and bacteriostatic effects against periodontal pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia* and *Bacteroides forsythus* [32]. However, one common problem encountered with most peptides is their relatively low stability. The physicochemical properties of many peptides make it difficult to obtain satisfactory formulations, in particular, since inactivation is possible during their incorporation into the controlled release system.

2.1.4. Tetracyclines

The tetracyclines are a group of broad-spectrum antimicrobial agents that were introduced into clinical practice in the late 1940s. There are now numerous compounds on the market, all based on the congeneric derivatives of the polycyclic naphthacene carboxamide [53].

Tetracycline, doxycycline and minocycline are used extensively in the management of periodontal diseases. They are bacteriostatic antibiotics which interfere with bacterial protein synthesis and also inhibit tissue collagenase activity [54]. They have a broad spectrum of activity inhibiting both Gram negative and Gram positive organisms, including the beta-lactamase producing strains which occur in approximately 50% of 6–7 mm deep periodontal pockets and against which penicillins are ineffective. Tetracycline analogues such as doxycycline and minocycline, although more expensive, have a number of theoretical advantages over tetracycline. They exhibit greater oral absorption, they have more prolonged half-lives, and they show enhanced lipid solubility, which is important for their antibacterial action [53].

In the case of tetracycline, it has been shown to be retained on the root surface after irrigation of periodontal pockets in vivo and to be able to subsequently inhibit bacterial growth in vitro for 16 days [55,56]. Tetracycline solutions also exhibited high substantivity in the periodontal environment with half times of 4.4 and 12.2 h (1 and 10% solutions), 250 and 700 times longer than the expected half times of 0.017 h for a non-substantive substance [37,57]. This property could be related to the formation of less soluble calcium-tetracycline complexes as a result of partial dissolution of the hydroxyapatite of cementum or dentin at lower pH levels [58].

It is now well established that the tetracyclines have anticollagenase properties which are unrelated to the drug's antibacterial activity [54,59,60]. Doxycycline is the most potent tetracycline for collagenase inhibition [53]. It has been suggested that such activity relates to the drug's ability to bind with calcium and zinc ions. A further mechanism may be associated with the ability of tetracyclines to scavenge reactive oxygen radicals produced by neutrophils. The inhibitory effect of tetracycline on oxygen radicals may also prevent a wider spectrum of tissue destruction. Thus, tetracyclines may have general antiproteolytic properties.

After completion of tetracycline therapy, there is first a reduction in the periodontopathic microflora followed by a return to the pre-treatment composition if scaling and root planing have not been carried out prior to medication. One of the major concerns about antibiotic usage, particularly in long-term low dosage regimes, is that bacteria may develop

resistance to the antibiotic [61]. Most of the subgingival microorganisms are susceptible to tetracycline at a minimum inhibitory concentration (MIC) of $\leq$1–2 μg/ml. However, species such as *Eikenella corrodens*, *Prevotella oralis*, *Selenomonas sputigena* and some strains of *Campylobacter* and *Veillonella* exhibited intrinsic tetracycline resistance (MIC $\geq$ 16 μg/ml) [53,61]. Microorganisms associated with periodontitis can also develop a resistance after exposure to subinhibitory concentrations of antibiotics [62,63].

2.1.5. Metronidazole

Among the antibiotics that have been considered for periodontal treatment, metronidazole has often been chosen because of its selective efficacy against obligate anaerobes [10]. Metronidazole acts by inhibiting DNA synthesis. It is known to convert into a reactive reduced form and affects specifically anaerobic rods and spirochetes in the subgingival microflora.

Metronidazole, long known to be ineffective in vitro against *Actinobacillus actinomycetemcomitans* was marginally more effective than tetracycline in the treatment of juvenile periodontitis, a disease considered to be associated with the former organism [64]. This emphasizes the multiinfectious character of periodontal disease where in vitro tests do not necessarily reflect in vivo effect [36]. Metronidazole has also been successful in refractory and advanced cases when used for a 1-week period [31]. Other studies reported that adjunctive metronidazole therapy was more effective in adults with deep pockets than with less advanced periodontitis [37]. In one study, without a thorough maintenance therapy, the beneficial effects observed in deep sites 3 months after adjunctive metronidazole were no longer apparent after 3 years [65]. However, sites with a moderate level of disease at baseline demonstrated an improvement after 3 years which was not present after 3 months. The reason for this finding is unclear but highlights the need for clinical trials of long duration since antibiotics often produce improvements in microbiological and clinical parameters which tend to drift towards control levels with time.

2.1.6. Clindamycin

Clindamycin has been investigated for treatment of periodontal disease in a limited number of studies [66,67]. Systemic clindamycin therapy, as an adjunct to scaling, decreased the incidence of active disease from an annual rate of 8.0 to 0.5% of sites per patient [68,69]. However, clindamycin did not permanently suppress subgingival *Porphyromonas gingivalis* [70], which may explain the recurrence of disease activity in some patients. Following gel insertion of clindamycin in conjunction with subgingival scaling, motile rods and spirochetes were not detected after 1 month. *Prevotella intermedia* and *Porphyromonas gingivalis* were eliminated or below detectable levels after 1 week post-therapy but were again detected at 12 weeks [67].

2.1.7. Ofloxacin

Ofloxacin is a newly developed synthetic pyridone carboxylic acid (PCA) derivative. Although the earlier PCA derivatives were not active against Gram positive bacteria and anaerobes, ofloxacin can kill Gram positive bacteria and anaerobic bacteria [71]. This action is absent or very weak in the earlier antibiotic, i.e. erythromycin, tetracycline and clindamycin. Ofloxacin showed marked antibacterial activity against periodontopathic bacteria including Bacteroides species, Fusobacterium species and *Actinobacillus actinomycetemcomitans*. Furthermore, ofloxacin has high chemical stability and adverse effects have rarely been reported.

2.2. Periodontal local delivery devices

Local delivery devices were widely studied for various applications. Table 3 includes a list of advantages and potential disadvantages of controlled release devices.

Regardless of the carrier system used, a candidate polymer for the design of a controlled delivery system must comply with a range of characteristics valid for most biomaterials: (i) it must be free of elutable impurities, additives, stabilizers, catalyst residues, and emulsifiers; (ii) with the exception of bioerodible systems, the physical, chemical, and mechanical properties of the polymer should not be altered by the biological environment; (iii) it must have sufficient mechanical and thermal stability; (iv) it must be able to be readily processed, cast, or molded in films, rods, tubings, and so forth; (v) the material should not be carcinogenic, toxic, or inflammatory; (vi) the system must be able to be sterilized or prepared under aseptic conditions.

A wide variety of specialized local delivery systems (i.e. intrapocket devices) have been designed to maintain the antibiotic in the GCF at a concentration higher than the MIC. Fibers, films, strips and microparticles made of biodegradable or non-biodegradable polymers have been reported as effective methods to administer antibacterial agents for periodontal therapy. Together with these solid devices, semi-solid adhesive or non-adhesive formulations have also been proposed (Table 1).

2.2.1. Fibers

2.2.1.1. Hollow fibers The reservoirs without rate control delivery include devices such as hollow fibers filled with a therapeutic agent in which the agent is released simply by diffusion through the reservoir wall [18].

Goodson's first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline [72]. These fibers released tetracycline at a first order rate with 95% of the drug released in the first 2 h. Although GCF levels of tetracycline remained in the therapeutic range for 24 h and some effects on spirochetes were reported, the study should be viewed primarily as an evaluation of drug delivery.

Hollow fiber systems that have been used in periodontal pockets have been shown to release the drug so rapidly that

Table 3
Main advantages and potential disadvantages of controlled delivery systems (CDS) for the treatment of periodontitis

Advantages of CDS	Disadvantages of CDS
Maintenance of drug levels in a therapeutically desirable range	Toxicity or lack of biocompatibility of the polymer material
Reduction or elimination of harmful side effects of drugs	Pain caused by the presence of the implant
Protection from degradation of drugs with short in vivo half-lives	Production of harmful by-products from a polymer if it is biodegradable
Improved patient compliance	Need of surgical procedure to implant the device in the appropriate location
Elimination of patient discomfort compared to parenteral administration	Expense of a particular polymer-drug formulation
Improved drug administration in geographic areas with low medical supervision	

they would be qualified only marginally as sustained-release devices.

2.2.1.2. Ethylene vinyl acetate fibers After noting the poor control of drug release from hollow fibers, Goodson evaluated the delivery of tetracycline incorporated into different polymers such as polyethylene, polypropylene, polycaprolactone, polyurethane, cellulose acetate propionate and ethylene vinyl acetate (EVA) [73]. EVA was found to be flexible and to allow drug delivery for up to 9 days in vitro. The EVA fibers containing 25% tetracycline hydrochloride commercialized under the trademark Actisite® (Alza Corporation, Palo Alto, CA, USA) were placed circumferentially into the pockets with an applicator, and secured with cyanoacrylate adhesive [74]. The EVA fibers maintained constant drug levels in GCF of periodontal pockets above 600 μg/ml throughout day 10 [57]. This contrasts with the non-linear release characteristics of the fiber observed in vitro. The decay kinetics of the tetracycline concentration in the GCF following fiber removal were similar to those obtained from 1% subgingival irrigation. This suggests that the tetracycline in the GCF following tetracycline fiber application was in equilibrium with the same binding sites occupied by tetracycline following 1% irrigation.

A multi-center clinical study reported that the numbers and proportions of detectable pathogens (with the exception of *Porphyromonas gingivalis*) varied over time and exhibited three distinct phases: a rapid decrease in the proportions of pathogens immediately after therapy followed by an increase 1–3 months post-therapy and then a spontaneous decline over the 3–12 month period following therapy [75] (Fig. 2). This response was particularly prominent with *Eikenella corrodens*. The return to higher levels of pathogens was attributed to either recolonization or regrowth from incompletely eliminated microorganisms in the pocket. Two mechanisms could account for the spontaneous reduction in the number of pathogens during the following 3–12 months. The first is that host response mechanisms can operate more effectively under conditions of reduced bacterial load. Indeed there is evidence that systemic antibody levels to periodontal pathogens are often elevated after scaling. A second hypothesis is that the local changes of the microbial ecology may have led to environmental conditions unfavorable for sustaining growth of periodontal pathogens.

A study conducted on 121 sites in 20 patients evaluated the safety and clinical efficacy of tetracycline fibers applied for 10 days after scaling and root planing [17]. Analysis of data from all sites indicated that a significant decrease in probing depth and gain in attachment were present at all follow-up visits (i.e. 1, 3 and 6 months). The proportion of bleeding pockets was reduced from 77 to 27% during the experimental period.

Periodontal disease recurrence from 3 to 12 months following various treatments with scaling and root planing and controlled-release tetracycline fibers (Actisite®) was also investigated in 122 adult volunteers with at least one bleeding pocket ≥5 mm in each of four quadrants [74]. Quadrants were randomly assigned to receive one of four treatments: scaling and root planing (S); scaling and root planing plus tetracycline fiber for 10 days (SF); fiber therapy alone for 10 days (F); or fiber therapy alone for 20 days (FF). Disease recurrence was defined as ≥1 mm mean attachment loss at a site during the 3–12 month period. Sites treated with SF experienced significantly less disease recurrence (4%) than S, F, or FF (9, 10 and 12%, respectively). The

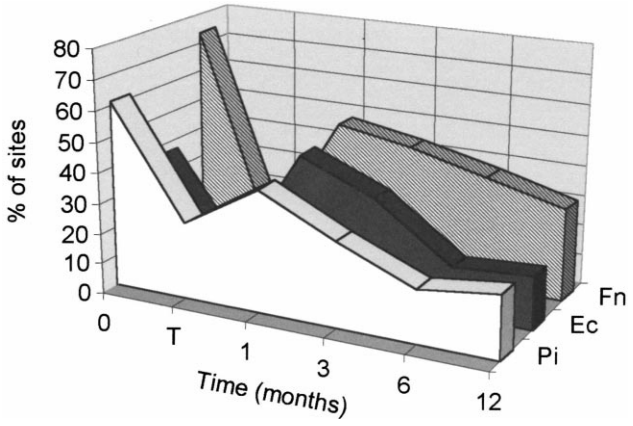

Fig. 2. Proportion of sites with detectable levels of *Fusobacterium nucleatum* (*Fn*), *Eikenella corrodens* (*Ec*) and *Prevotella intermedia* (*Pi*) for sites treated with scaling and root planing plus tetracycline fibers over time. Reprinted with permission.

ability of locally-delivered tetracycline to prevent disease recurrence may be related to the effects of the drug bound to the root surface even if tetracycline was not detected in GCF after fiber removal. Studies reported no substantial differences in clinical response [76] or microbiological response [75] between a single tetracycline fiber application and serial tetracycline fiber applications. It was concluded that a single 10 ± 2 days application of tetracycline fibers was generally sufficient to obtain full benefit from this form of treatment when scaling and root planing were performed prior to the fiber application.

In addition to the extensive evaluation of drug delivery kinetics from the EVA fibers, this system has undergone numerous clinical trials to test its efficacy in the treatment of periodontal disease. Studies that were well-conducted and apparently well-controlled have demonstrated the clinical efficacy of these fibers. However, their actual value in patient therapy has been somewhat difficult to interpret because clinicians have found the fiber placement technique challenging, and a considerable percentage of fibers become dislodged during the course of the 10-day treatment period [77]. In a study enrolling 122 patients from three dental centers, ten adverse events related to the fiber treatment were reported including three cases of oral candidiasis and among the seven remaining, severe gingival redness, tongue pigmentation and glossitis [76]. In addition, at fiber removal, various degrees of gingival redness were observed in 66% of patients on day 10 and in 77% of patients on day 20 in the two 10-day serial fiber applications quadrant. In this study, the patient's treatment evaluation summary was also evaluated and showed that 26.7% experienced discomfort during fiber placement, 19.8% reported pain on fiber removal and 31.6% of patients would choose to use local anesthesia during fiber placement. Another disadvantage of tetracycline fibers is that fiber insertion appeared to be time-consuming even when the operator was familiar with the procedure. The average insertion time per tooth was 15.5 min [17].

2.2.2. Strips and compacts

Larsen studied in vitro release of doxycycline from different bioabsorbable materials and acrylic strips [78]. The absorbable materials used in this study included Surgicel, a hemostatic gauze made of oxidized regenerated cellulose, CollaCote, a collagen wound dressing, and Tissel, a fibrin sealant. Doxycycline loading was 40% (w/w) for all the formulations. Surgicel produced very high concentrations, above 250 μg/ml, throughout the study. The acrylic strip and CollaCote decreased to low levels of both concentration and residual antibacterial activity in a few days. Tissel was intermediate with a continuous decrease in concentration but rather high level of residual activity throughout the study. The physical properties of the acrylic strip changed in serum where the surface of the strip was dissolved. This property, combined with a noticed tendency of the material to disintegrate during preparation, may involve the risk of leaving injurious acrylic material in the periodontal pocket upon removal of the strip. Even the removal of the strip after therapy may cause damage to regenerating tissue at the site. This risk is avoided when using bioabsorbable materials.

Strips containing 25% tetracycline hydrochloride or metronidazole in poly(hydroxybutyric acid) (PHBA) as a biodegradable polymer matrix showed sustained release over 4–5 days with a significant burst effect at day 1 [79]. A favorable alteration occurred in the microbial flora of pockets treated with strips containing metronidazole compared to those treated by root planing. In treated sites, the proportion of cocci increased while the Gram negative rods, fusiforms and spirochetes decreased. The clinical improvement was of short duration as the results were not maintained over time once the active treatment was terminated.

The same authors reported on studies with compacts based on PHBA containing tetracycline hydrochloride [80]. They studied the effect of drug loading and polymer average molecular weight on the release rate of the drug. With the compacts containing 50% (w/w) of tetracycline, the mean drug concentration obtained was in the therapeutic range over the 10 days study period. This study also showed that clinical improvement was not maintained when treatment was stopped.

A controlled release strip coded PT-01 and made of poly (methacrylic acid) and hydroxypropyl-cellulose containing 10% ofloxacin has been reported by Kimura et al. [71]. Data showed that ofloxacin could be found in higher concentrations than the MIC of most periodontopathic bacteria in GCF over 7 days by a single application of PT-01 in the human periodontal pocket. Although the weekly application of PT-01 on days 0–35 showed some further shift in the proportion and reduction in subgingival microorganisms, statistically no significant differences in the microbiological results between the strip group and the control groups were found. Consequently, the authors suggested that the application of PT-01 might have a beneficial effect as an adjunct in conventional periodontal therapy.

The controlled release strips that gave the most interesting and long-term clinical improvement were chlorhexidine strips [18]. Controlled trials involving chlorhexidine in ethylcellulose strips used every 3 months in place of routine supportive periodontal therapy have shown significant clinical benefit for up to 2 years.

So far, no product has been marketed because of the non-biodegradation of the polymeric carriers or the only temporary clinical improvements after treatment completion.

2.2.3. Films

Films made of Eudragit® L and Eudragit® S, two water soluble poly(methacrylic acid-co-methyl methacrylate), and Eudragit® RL, a non-water soluble polymer poly(ethyl methacrylate-co-chlorotrimethyl ammonium methyl methacrylate), were developed by Higashi et al. [66] for the delivery of clindamycin. In vitro release study showed that

insoluble films release drug by diffusion and soluble films release drug by dissolution of the carrier. The in vivo drug release rate in periodontal pockets of beagles was lower than the in vitro rate. Depending on the matrix composition and drug release mechanism, total drug release varies from 1 to 100 h. Clindamycin concentration in the GCF was maintained at a constant level for 24–72 h. The time of drug release for such devices is too low for further clinical studies.

Some natural biodegradable polymers have been used for controlled release of antibacterial agents in the treatment of periodontitis. Sustained release devices composed of a cross-linked fish gelatin (Byco protein) containing chlorhexidine diacetate or chlorhexidine hydrochloride have been developed by Steinberg et al. [29]. The in vitro release profile of chlorhexidine from such degradable films is dependent on the amount of chlorhexidine incorporated into the film, by the cross-link density of the polymer and by the chlorhexidine salt used. The time of total drug release is short and varies from 4 to 80 h.

Another natural biodegradable polymer studied for controlled release of antibacterial agent was proposed by Minabe et al. [30]. This local delivery system is based on atelocollagen preparations with immobilized tetracycline. Collagen film treated by cross-linking and containing tetracycline showed an amount of tetracycline exceeding the effective dose ($\geq$8 μg/ml) in the GCF, even on day 10 after insertion of the preparation.

Films based on synthetic biodegradable polymers such as poly(lactide-co-glycolide) (PLGA) containing tetracycline have been developed for modulated release of the drug [81]. Drug loading in such films was only 5% (w/w), which seems too low to reach the MIC once placed into the periodontal pocket.

In another study, PLGA films containing 25% of tetracycline hydrochloride were evaluated in vitro and on human patients [82]. In vitro study showed an incomplete release of tetracycline; only 30–60% of total tetracycline was released. This result was explained by the presence of drug particles entrapped within the hydrophobic, PLGA matrix. Another explanation could be the degradation of tetracycline into the release medium at 37°C. In this study, the PLGA films showed a poor retention in the periodontal pockets and were secured around the tooth with a silk suture and cemented with cyanoacrylate adhesive. Preliminary results from eight patients indicate that the therapeutic drug concentrations, in excess of the MIC, were maintained in the GCF for a period of at least 14 days.

Among synthetic biodegradable polymers used as films for controlled release of antimicrobial agents, systems based on poly(ortho esters) have also been studied for the delivery of metronidazole [83]. The in vitro study showed the influence of drug loading, film thickness and oleic acid content on drug release rate and profile. No study on patients has been reported so far.

Ethyl cellulose films containing either 20% metronidazole or 20% chlorhexidine were compared to short-term use of systemic antibiotherapy in patients with advanced forms of periodontal disease in order to prevent the normally necessary access surgery [31]. All teeth treated with the ethyl cellulose films were scaled just before the insertion of the films. There was a 93% reduction in the need for periodontal surgery for individual teeth and an 81% reduction in the need for tooth extractions.

More recently, a new film composed of cross-linked hydrolyzed gelatin and glycerin for local delivery of chlorhexidine digluconate has been developed and commercialized under the trademark Periochip® (Perio Products Ltd, Jerusalem, Israel) [38]. This biodegradable film showed an initial burst effect in the first 24 h, whereby 40% of chlorhexidine was released, probably due to diffusion, followed by a constant slower release over about 7 days, occurring partially in parallel with enzymatic degradation of the film. An in vivo study on 12 patients reported chlorhexidine concentrations of 800–1000 μg/ml in the GCF in the first 48 h after the Periochip® placement. This first burst was followed by lower concentrations of 100–500 μg/ml over the next 6 days. Concentrations above the MIC for most pathogens (150 μg/ml) were seen for at least 7 days. Compared to scaling and root planing alone, Periochip® treatment adjunctive to scaling and root planing showed significant reduction in the probing pocket depth, a gain in attachment level for pockets $>$7 mm at 6 months and a decrease in the gingival index and in bleeding on probing at 3 months. This film 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.

2.2.4. Injectable systems

Injectable systems are particularly attractive for the delivery of antibiotic agents into the periodontal pocket. The application can be easily and rapidly carried out, without pain, by using a syringe. Thus, the cost of the therapy is considerably reduced compared to devices that need time to be placed and secured. Moreover, an injectable delivery system should be able to fill the pocket, thus reaching a large proportion of pathogens.

Two types of injectable delivery systems have been assessed in the treatment of periodontal diseases, biodegradable microparticles and gels.

2.2.4.1. Microparticles Microparticles based on biodegradable poly(α-hydroxyacids) such as poly(lactide) (PLA) or poly(lactide-co-glycolide) (PLGA) containing tetracycline have been designed for periodontal disease therapy [84]. The in vitro tetracycline release rate is influenced by the polymer choice (lactide/glycolide ratio, polymer molecular weight and crystallinity) and by the pH of the medium; the tetracycline release rate is increased as the pH increases. PLGA microspheres have also been proposed for the delivery of histatins [85].

Peptide released from microspheres prepared without additive was not bioactive. The stability of the peptide has been maintained at 100% throughout the release by the addition of non-ionic surfactant. In vitro release of total peptide lasts 1 month. Although these in vitro studies seem promising, because drugs are slowly released in a controlled manner over a period of 2 weeks to 1 month, some questions related to the retention of such formulations in the periodontal pocket need clarification.

PLGA microspheres containing minocycline were evaluated alone or as an adjunct to scaling and root planing, in comparison to scaling and root planing alone or to no subgingival treatment in adult periodontitis [86]. Data showed that probing depth reduction with treatment plus scaling and root planing was significantly greater than all other groups at 1 month. However, there were no differences in probing depth reduction among the groups at 6 months. Unfortunately, no changes in levels of attachment were reported which both precludes direct comparison to other studies and provides little indication on the progression of periodontitis. The minocycline local delivery system, both with or without scaling and root planing, achieved a significant reduction in *Porphyromonas gingivalis* 1 month after therapy. Although these results suggest some interesting potential for this therapy, one must always be cautious in extrapolating findings from studies with a small sample size.

2.2.4.2. Gels Mucoadhesive, metronidazole-containing gel systems designed for periodontal treatment and based on hydroxyethylcellulose, Carbopol 974P and Polycarbophil have been described [87]. In vitro drug release was significantly decreased as the concentration of each polymeric component was increased, due to both the concomitant increased viscosity of the formulation and additionally, the swelling kinetics of polycarbophil following contact with dissolution fluid. Increasing the concentrations of each polymeric component significantly increased formulation hardness, compressibility, adhesiveness and syringeability due to polymeric effects on formulation viscosity. The optimal choice of bioadhesive formulation for use in periodontal disease will involve a compromise between achieving the necessary release rate of the drug and the mechanical characteristics of the formulation.

Bioadhesive semi-solid systems based on hydroxyethylcellulose (HEC) and polyvinylpyrrolidone (PVP) containing tetracycline were studied for their mechanical properties and drug release rates [88]. Data showed that increased concentrations of HEC decreased the rate of release of tetracycline, due to the concomitant increase in product viscosity and the subsequent decreased rate of penetration of dissolution fluid into the formulation. Conversely, an increased PVP concentration increased tetracycline release rates, due to an increased formulation porosity following dissolution of this polymer. Increased concentrations of HEC and PVP increased the hardness, compressibility and work of syringeability of semi-solid formulations and also their adhesiveness. This example shows again the interactions between the different physical properties of adhesive formulations. Due to unacceptably high product viscosity and syringeability, a number of formulations studied were inappropriate for clinical examination.

A mucoadhesive gel formulation based on 4% Carbopol containing 1% clindamycin hydrochloride was evaluated in vivo on microbial flora of periodontal pockets deeper than 5 mm [67]. Active and placebo gels were inserted once a week for 2 weeks in sites that received subgingival scaling and root planing. Changes in the microbial content of the periodontal pockets treated by subgingival scaling and 1% clindamycin gel were significant, compared with negative controls, particularly with respect to anaerobic black-pigmented bacteria and the motile gram-negative flora. However, after 3 months, most of the treated cases were recolonized by the same initial species. Unfortunately, no clinical data were presented; therefore, no correlation between changes in the flora and changes in disease patterns could be made.

Recently, a gel formulation based on 2.5% hydroxypropylmethylcellulose containing 0.125% histatin was studied in vivo in beagle dogs by Paquette et al. [32]. Active and placebo formulations were tested for 10 weeks and applied twice daily around premolar teeth. It was reported that beagles treated with active gel demonstrated significantly lower plaque index scores at day 42, significantly lower gingival index scores from day 21 through 42, and a significantly lower percentage of bleeding on probing scores at days 14 and 28 compared to beagles treated with placebo gel. In spite of the positive clinical results, the twice daily applications of gels can not be qualified as controlled or sustained release.

An injectable lipid-like vehicle based on glycerol monooleate and sesame oil containing 25% metronidazole (Elyzol®) (Dumex-Alpharma, Copenhagen, Denmark) has become available with supportive evidence of efficacy. This product is syringed into the pocket area where the initially thixotropic carrier thickens into a gel [10]. According to the manufacturer, the formation of highly viscous liquid crystals when the formulation is in contact with water is responsible for this effect. Therapeutic levels of metronidazole are reported for a period of 2–3 days and the agent should be used twice in 3 weeks. Data indicate that local metronidazole gel in combination with scaling and root planing seems to be more effective in terms of producing both clinical and microbiological improvements compared to pure mechanical and pure metronidazole treatments. Controversial results reported in another study do not support the routine use of adjunctive Elyzol® in the non-surgical treatment of periodontitis because of the poor clinical and microbiological efficacy compared to scaling and root planing alone [26]. This is probably due to the rapid elimination of Elyzol® gel from the periodontal pocket [89].

Two other semi-solid lipid-like formulations based on

poly(oxyethylene-co-oxypropylene) (poloxamer) and glycerol monooleate were developed for tetracycline release by Esposito et al. [90]. These two formulations are characterized by a solid-gel transition and become semi-solid once in the periodontal pocket. After 7 h, in vitro tetracycline release was 18% and 65% of the entrapped drug for monoglyceride and poloxamer gels, respectively. In vivo retention results reported that the persistence of monoglyceride gel is more prolonged than that of poloxamer gel. This later disappeared after 1 h while monoglyceride gel was still retained after 8 h. A short-term split mouth clinical trial indicated that the subgingival application of both gels in conjunction with scaling and root planing produced clinically and statistically significant improvement outcome in moderate to deep periodontal pockets. Surprisingly, in spite of the rapid drug release and the poor retention of such gels, positive clinical results were obtained.

Gel formulations containing 2% minocycline have been commercialized under several trademarks; Periocline® (Sunstar Co. Ltd., Osaka, Japan) [91,92] and Dentomycin® (Lederle Laboratories, UK) [93]. The gel is composed of hydroxyethylcellulose, aminoalkyl-methacrylate copolymer, triacetine, magnesium chloride and glycerynum concentratum. Several investigations on clinical and microbiological effects of this gel in beagles or in humans have been reported. Administration of Periocline® after scaling and root planing was performed once a week for 4 consecutive weeks. At week 4, proportions of *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* were significantly decreased in treated sites. *Prevotella intermedia* was detected from seven of 22 sites at week 4 and 16 sites at week 12 in treated sites. Minocycline treated sites were also associated with a significant decrease in probing depth and bleeding on probing compared with those of control sites at week 4.

A study using Dentomycin® gel has recently reported that this adjunctive formulation provided a more advantageous outcome for non-surgical periodontal treatment in terms of attachment level and bleeding on probing [93].

In a study enrolling 54 patients with four pockets ≥5 mm and bleeding on probing, the efficacy of three commercialized available periodontal systems for local delivery of antibiotics as adjuncts to scaling and root planing was evaluated [94]. The four treatment groups included scaling and root planing alone, scaling and root planing plus application of 25% tetracycline fiber (Actisite®), scaling and root planing plus application of 2% minocycline gel (Dentomycin®) and scaling and root planing plus application of 25% metronidazole gel (Elyzol®). Clinical measurements were taken at baseline and 6 weeks after the end of treatment periods. The improvements in clinical parameters were greater than scaling and root planing alone in all three adjunctive treatment groups. The probing depth reduction was significantly greater in the scaling plus tetracycline fiber group (1.35 mm) than the scaling and root planing alone group (0.6 mm). The difference between groups in the improvement of the attachment level or bleeding on probing was not significant. Scaling plus tetracycline fiber treatment resulted in the greatest reduction in the gingival index scores. The frequency of sites with suppuration was markedly reduced following all treatments. The application of tetracycline fibers was markedly more time consuming than other treatments. Considering the time and cost involved in using different locally delivered antimicrobial systems, using these agents does not seem justified as part of initial periodontal therapy. Instead, a scenario was suggested whereby following initial phase therapy, tetracycline fibers could be used in place of surgery for sites with remaining severe disease, whereas the other systems might be applicable in less severe cases.

Another injectable biodegradable delivery system containing 10% doxycycline hyclate (Atrigel®) (Atrix Laboratories, Fort Collins, CO, USA) was widely studied. This system is based on a biodegradable polyester poly(DL-lactide) dissolved in a biocompatible solvent *N*-methyl-2-pyrrolidone (NMP) [51,95,96]. This drug delivery system is particularly suited to periodontal use because the system has a viscosity such that it can pass through a cannula into a periodontal pocket where it solidifies in situ to deliver the therapeutic agent over 7 days. The analyses of the bioactive doxycycline levels into the GCF showed a level of 250 μg/ml during a period of 7 days. Interestingly, levels of 10–20 μg/ml were still present for 3–5 days after the polymer had been removed [97]. It is possible that these doxycycline levels were due to minute particles of polymer remaining within the pockets or to the substantive effects of tetracyclines within the periodontal pocket-adjacent-tooth-surface environment. In the doxycycline-treated group, the clinical reduction in bleeding on probing, in probing depth, and gain in attachment level were substantial and consistent with a reduction of inflammation in the adjacent gingival tissues.

In another study, Atrigel® containing 5% sanguinarine was compared to vehicle control, scaling and root planing and supragingival plaque control in the treatment of adult periodontitis [52]. Data reported that sanguinarine was superior to vehicle control in deep pockets only. Sanguinarine failed to demonstrate superiority over vehicle control on a consistent basis. The clinical response to so-called negative controls consisting of tooth brushing and flossing gave surprisingly significant positive changes from baseline for all clinical parameters. The effects of vehicle control alone in this trial were also significant for all clinical parameters in spite of their lower retention rate compared to sanguinarine. The positive effect of the vehicle alone was also described for biodegradable films made of poly(lactide-co-glycolide) [82]. This could be attributed to the clinical effectiveness inherent in the controls or the low activity of the sanguinarine in the delivery system.

These findings have been recently confirmed in a human clinical trial [51]. A comparative study using the same Atrigel® delivery system containing either 10% doxycycline

Table 4
Selected clinical trials using local controlled delivery systems for antimicrobial agents[a]

Drug delivery system	Antimicrobial drug	Number of patients	No therapy	CV	SRP + CV	SRP	DDS	SRP + DDS	Duration of treatment	Reference
EVA fibers, Actisite®	Tetracycline	122 → 116[b]	No	No	No	Yes	Yes	Yes	10 days × 1	[76] Drisko et al., 1995
Actisite®	Tetracycline	31	No	No	No	Yes	Yes	Yes	10 days × 1	[75] Lowenguth et al., 1995
PT-01 inserts	Ofloxacin	31 → 27	No	No	Yes	Yes	No	Yes	35 days × 6	[71] Kimura et al., 1991
Adhesive inserts, Periochip®	Chlorhexidine	118	No	No	No	Yes	No	Yes	10 days × 1	[38] Goffin, 1998
Microspheres	Minocycline	51 → 39	Yes	No	No	Yes	Yes	Yes	ND × 1	[86] Jones et al., 1994
Minocycline gel, Periocline®	Minocycline	11	No	No	No	Yes	No	Yes	28 days × 4	[91] Nakagawa et al., 1991
Minocycline gel, Dentomycin®	Minocycline	30 → 24	No	No	Yes	No	No	Yes	28 days × 4	[93] Graça et al., 1997
Bioadhesive gel	Clindamycin	20	No	No	Yes	No	No	Yes	14 days × 2	[67] Sauvetre et al., 1993
Metronidazole gel, Elyzole®	Metronidazole	10	Yes	No	No	Yes	Yes	Yes	14 days × 2	[10] Noyan et al., 1997
Liquid system, Atrigel®	Doxycycline, sanguinarine	180 → 170	No	Yes	No	No	Yes	No	7 days × 1	[96] Polson et al., 1997

[a] CV, control vehicle without drug; SRP, scaling and root planing; DDS, drug delivery system.
[b] Number of patients enrolled in the study → number of patients who completed the study.

hyclate or 5% sanguinarine hydrochloride reported that both clinical and statistical superiority were observed in the doxycycline group for all parameters when compared to the formulation containing sanguinarine and the vehicle alone. Most of the changes in clinical parameters from baseline were maintained over the first 4 months. The reapplication of doxycycline formulation at month 4 produced some additional positive changes in attachment level gain, probing depth reduction and bleeding on probing reduction.

Recently, the Atrigel® delivery system for controlled release of 8.5% doxycycline has been approved by the FDA for commercialization under the trademark Atridox™.

3. Evaluation of local delivery devices in periodontics

Studies dealing with local delivery devices vary considerably in regards to the selection of patients, the treatments provided, the duration of the study and the microbiological and clinical parameters used.

3.1. Experimental design

Although many publications on the local delivery concept have appeared in the periodontal literature since the late 1970s, there are surprisingly few studies that demonstrate clinical efficacy using controlled release local delivery systems in periodontitis patients. The vast majority of studies reported to date have involved the first two stages of defining the delivery system and demonstrating potential therapeutic value, i.e. proving the concept. Table 4 summarizes the experimental designs for some clinical trials that used controlled release locally delivered antimicrobials. Comparison between reports is not straightforward since their treatment patterns differ widely. In some studies the device is used as the only treatment for each site, but more commonly they are used adjunctively. Similarly, the control sites to which the device effects are compared vary in type or may be absent.

3.2. Microbiological evaluation

In recent years, it has been accepted that a variety of suspected pathogens have been important etiological factors in the breakdown of periodontal tissues. These pathogens include anaerobic Gram negative species such as *Porphyromonas gingivalis* (*Pg*), *Prevotella intermedia* (*Pi*), *Bacteroides forsythus* (*Bf*), *Fusobacterium nucleatum* (*Fn*), *Selenomonas* and *Campylobacter* species and facultatively anaerobic Gram negative rods such as *Actinobacillus actinomycetemcomitans* (*Aa*) and *Eikenella corrodens* (*Ec*) [12,15].

It has been demonstrated that specific microorganisms are associated with the various forms of periodontal disease. *Aa* is often found in juvenile periodontitis and in refractory periodontal sites. It was reported that *Aa* could also be recovered from adult periodontal pockets. *Pg* and *Pi* are associated with adult periodontitis [75,91]. *Pg* was also isolated from both untreated and recurrent periodontal pockets (Table 1).

From Table 5, we note that in vitro effects of many antimicrobial agents against microorganisms do not always reflect the results in vivo when the antibiotic is incorporated into a local controlled delivery system. For example, in vitro, the sensitivity of *Pi* against minocycline is as high as *Pg*. However, in vivo, the controlled delivery device Periocline® showed greater and significant reduction of *Pg* compared to *Pi* [91].

The effects of controlled local therapies on the microflora appear to be transient. This may be due to inadequate supragingival plaque control as several studies have shown that treated sites are rapidly recolonized unless good oral hygiene is maintained [86].

4. Conclusion

Most reports regarding the recent periodontal literature on medical treatment have involved tetracyclines, metronidazole, or chlorhexidine. Although these therapeutic agents have been selected according to current knowledge of

Table 5
Susceptibility of suspected pathogens to various antimicrobial agents in vitro and to various controlled release formulations in vivo[a]

Microorganisms	MIC tetracycline	SRP + Actisite®	MIC minocycline	SRP + Periocline®	MIC metronidazole	SRP + Elyzole®
Actinobacillus actinomycetemcomitans	0.5–8	↓[b]	1–3	→	32	→
Porphyromonas gingivalis	2	↓↓	2	↓↓	<1–4	↓↓
Prevotella intermedia	6	↓	<1	↑	0.5–4	↓
Fusobacterium nucleatum	2	↓↓	1	ND	1	ND
Eikenella corrodens	3–32	↓	2–8	ND	>32–R	ND
Campylobacter rectus	2	↓↓	1	ND	2	ND

[a] MIC, minimal inhibitory concentration required to inhibit growth of 90% of strains expressed in μg/ml; SRP, scaling and root planing; R, resistant to >64 μg/ml; ND, not determined.

[b] ↓, decrease in proportion of microorganisms compared to baseline; ↓↓, strong decrease in proportion of microorganisms compared to baseline; →, no change in proportion of microorganisms compared to baseline; ↑, increase in proportion of microorganisms compared to baseline.

bacteria involved in periodontal diseases, the outcome of interest to manufacturers, regulatory agencies, practitioners, and patients is the clinical efficacy. These therapeutic systems have shown strong efficacy against periodontal microorganisms; however, it has been difficult to correlate the therapeutic improvements with microbiological results. Indeed, the type of microbial assay can dramatically influence the results observed with different therapies [18,75]. It should also be noticed in most of the local controlled release delivery systems studied that the level of antimicrobial agent released into the periodontal pocket far exceeds levels for antimicrobial activity. It is very likely therefore that these agents in such high concentrations exert multiple effects on the local environment, only one of which may be related to antimicrobial activity.

Despite the reported clinical successes, currently available controlled release formulations suffer from several disadvantages including: (i) the requirement for mechanical binding of the drug delivery system to a tooth surface to prevent removal of the system from the periodontal pocket as a result of the positive flow of GCF from the pocket into the oral cavity; indeed, the Atrigel® delivery system has to be maintained in the pocket by the addition of periodontal adhesive (Octyldent™) or periodontal dressing (Coe-Pak™ or Periocare®); (ii) the requirement for removal of tooth-bound, non-biodegradable drug delivery systems at the termination of treatment, as for Actisite® fibers; (iii) poor retention of oil-based delivery systems within the aqueous environment of the periodontal pocket as in the case of Elyzol®; (iv) potential deleterious effects of plasticizers leached from solid polymeric drug delivery systems on the periodontal tissues.

In conclusion, the publications dealing with efficacy studies suggest that the controlled delivery devices are a useful adjunct to conventional surgical or non-surgical treatments, but are no substitute for these measures. In particular, controlled delivery systems are of interest as an adjunct for recurrent and refractory periodontitis. Despite the large number of studies, there are insufficient comparative data to support any one of the local delivery systems as superior to another and several questions related to the optimal use of such new therapies remain.

First of all, clinical results appear not to be solely related to the bacterial susceptibility, giving rise to questions concerning the importance of the choice of the antimicrobial agent. Secondly, it appears that factors other than drug release kinetics are the major determinants of clinical outcome. Thus, do delivery systems differ in other ways than the convenience of their application? Moreover, although different systems are technically easy to use, operators reported some significant differences. Thus, the ease of use of systems in clinical practice is difficult to evaluate. Finally, great variability from site to site has been repeatedly noted by investigators showing that the same system could not work equally in all sites and in all patients. Answers to these different questions should allow an optimal treatment for each case of periodontal disease in the future.

Appendix A. Definitions

- Probing depth (PD): PD is defined as the distance from the gingival margin to the bottom of the pocket and is considered as a measure of the severity of periodontal disease.
- Clinical attachment level (CAL): CAL is defined as the distance from the cemento-enamel junction to the bottom of the pocket. The cemento-enamel junction or the limit of a restoration may be chosen as a reference point. Changes in attachment level and probing depth were monitored to assess the results of treatment or disease progression. CAL is considered as the primary measure of the efficacy of treatment.
- Gingival recession: recession, evaluated at the same location as the PD and the CAL, is the measure from the cemento-enamel junction to the gingival margin.
- Bleeding on probing (BOP): BOP in the depth of the pocket is recorded as present or absent. Sites that showed bleeding within 10–30 s following probing are scored as positive. The BOP score is expressed as the proportion (%) of bleeding sites out of the total number of experimental sites for each treatment group.
- Plaque and gingival indices (PI and GI): PI is used to evaluate the effectiveness of home care and GI is a measure of gingival inflammation. PI and GI are evaluated on a scale of 0 (no plaque or inflammation) to 3 (severe plaque or inflammation) at four sites (buccal, lingual, mesial and distal) of each tooth.

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