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Therapeutic strategies for effective management of periodontal disease.

Recent approaches for the treatment of periodontitis

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Periodontal disease is a localised inflammatory response caused by the infection of a periodontal pocket arising from the accumulation of subgingival plaque. Periodontal disease has been considered as a possible risk factor for other systemic diseases such as cardiovascular diseases and pre-term low birth weight infants. Advances in understanding the aetiology, epidemiology and microbiology of periodontal pocket flora have revolutionised the therapeutic strategies for the management of periodontal disease progression. This review summarises the recent developments in the field of intra-pocket drug delivery systems and identifies areas where further research may lead to a clinically effective intra-pocket delivery system.

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Periodontal disease is a collective term ascribed to several pathological conditions characterised by degeneration and inflammation of gums, periodontal ligaments, alveolar bone and dental cementum [1]. It is a localised inflammatory response caused by bacterial infection of a periodontal pocket associated with subgingival plaque [2]. Although bacteria are the primary cause of periodontal disease, the expression of microbial pathogenic factors alone may not be sufficient to cause periodontitis. Periodontal pathogens produce harmful by-products and enzymes that break extracellular matrices as well as host cell membranes to produce nutrients for their growth. In doing so, they initiate damage directly or indirectly by triggering host-mediated responses that lead to self-injury [1].

In the early phase of the disease (gingivitis), inflammation is confined to the gingiva but extends to deeper tissues in periodontitis, leading to gingival swelling, bleeding and bad breath. In the late phase of the disease, the supporting collagen of the periodontium is degenerated, alveolar bone begins to resorb and gingival epithelium migrates along the tooth surface forming a 'periodontal pocket' [2,3]. This periodontal pocket provides ideal conditions for the proliferation of microorganisms: primarily Gram negative, facultative anaerobic species. Prominent amongst these are *Bacteroides* spp.: *B. intermedius* and *B. gingivalis*; fusiform organisms: *Actinobacillus actinomycetemcomitans*, *Wolinella recta* and *Eikenella* spp.; and various bacilli and cocci; spirochetes; amoebas and trichomonads [2]. The periodontal pocket, however, remains and if it

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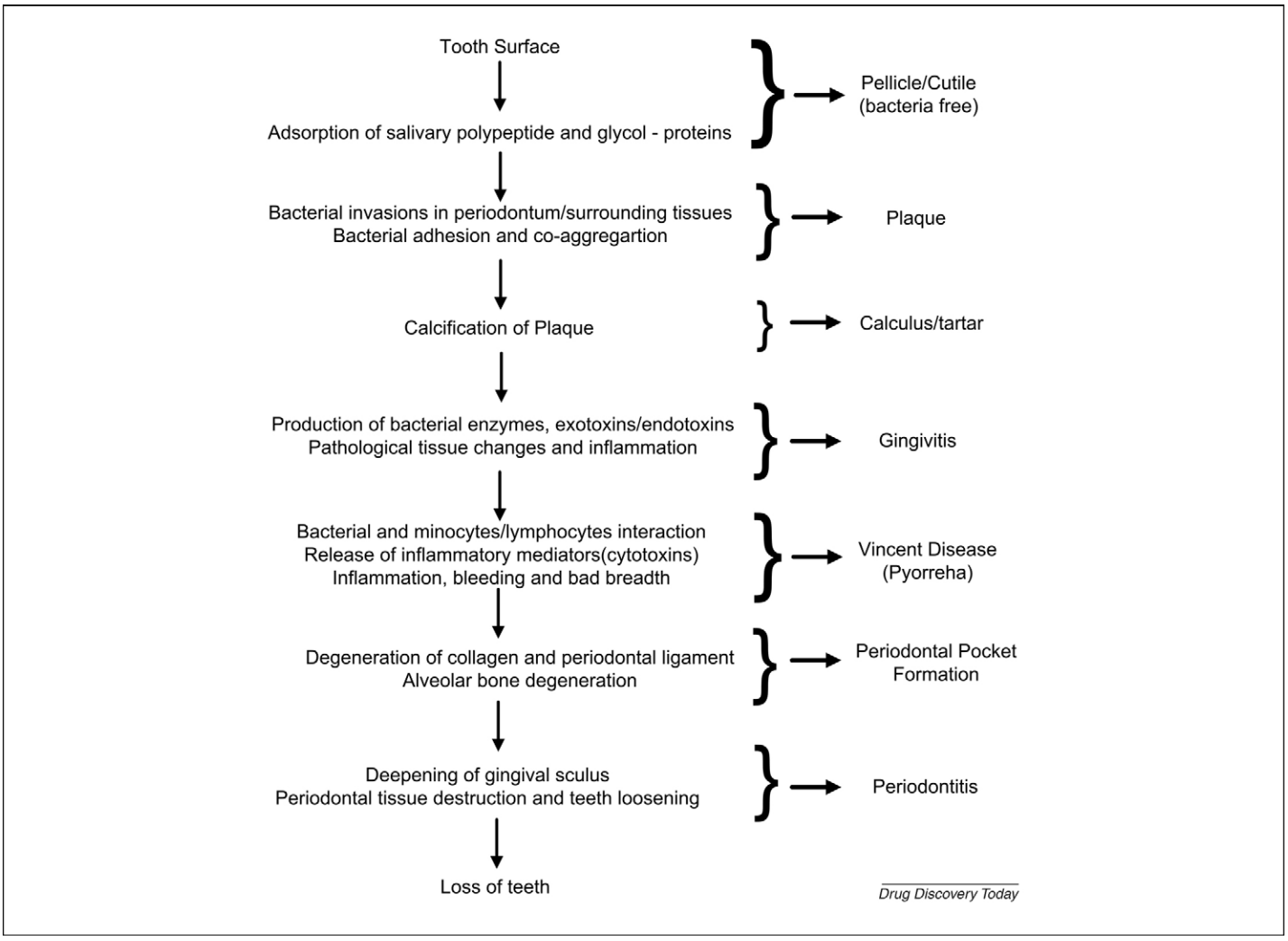

FIGURE 1

Flow chart representing pathogenesis of periodontal diseases. Formation of bacterial plaque; calcification of plaque; pathological and immunological manifestations resulting in gingivitis and periodontitis.

continues to harbour the bacteria associated with the disease, a potential for a further destructive phase exists. The disease may then require extensive treatment, failing which the teeth may be lost. Therefore, clearance of the subgingival infection and elimination of the periodontal pocket are considered a priority in the treatment of periodontitis. Figure 1 summarises the possible pathogenic mechanism of periodontal diseases, whereas various stages of periodontitis are represented in Fig. 2.

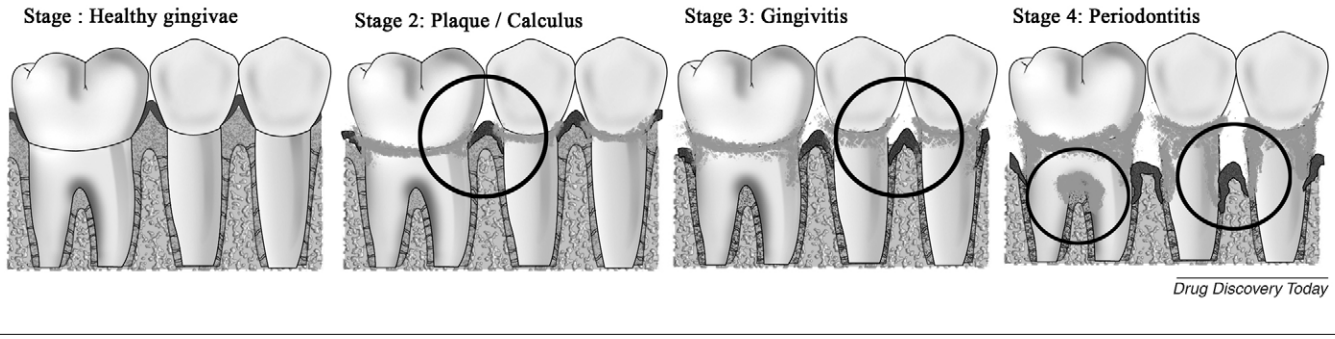

FIGURE 2

Diagrammatic representation of changes involved in the transition from healthy gingivae to the pathological periodontitis. Stage 1: healthy gum tissue (gingiva); Stage 2: plaque formation due to bacterial invasion; Stage 3: bacterial toxins irritate gums and trigger host-mediated responses that lead to gingivitis; Stage 4: destruction of gingiva and bone that support the tooth leading to periodontitis. This figure has been modified, with permission, from Ref. [3].

Advances in the understanding of the aetiology, epidemiology and microbiology of the periodontal pocket flora have revolutionised the therapeutic strategies for the management of periodontal disease progression [2,3]. The value of administering antimicrobial agents as an inexpensive and rapid means of augmenting mechanical periodontal debridement is worth consideration. The therapeutic success or failure depends not only on the antimicrobial activity of the chemotherapeutic agent but also on the location of infection, carrier system and route of administration [4]. This review highlights the current approaches to periodontal therapy and aims to identify areas where further research may lead to an effective treatment for periodontal infectious disease. This review also addresses practical problems regarding the use of currently available systems and summarises some key factors for the development of improved intra-pocket delivery systems approaching to ideal characteristics with a high degree of acceptance by the professionals as well as the patients.

Significance of intra-pocket drug delivery devices

The use of systemic antibiotic for the treatment of periodontitis has shown some beneficial effect [5,6]; however, in recent years systemic antibiotics are only recommended for the treatment of rapidly progressing or refractory periodontitis [4,7]. Multiple systemic doses of antibiotics have shown several drawbacks including: inadequate antibiotic concentration at the site of the periodontal pocket [8]; a rapid decline of the plasma antibiotic concentration to subtherapeutic levels [9]; development of microbial resistance; and high peak-plasma antibiotic concentrations, which may be associated with side effects [4]. These obvious disadvantages have evoked an interest in the development of novel intra-pocket drug delivery systems for the treatment of periodontal diseases [10].

The periodontal pocket results from the progression of periodontal disease. The characteristics of the gingival crevicular fluid (GCF), which fills the periodontal pocket, have been reviewed by Cimasoni [11]. Healthy sites are associated with small volumes (0.04 μl) and low flow rates (0.03 μl/min) and examination of the protein concentrations show it to be similar to extracellular fluid and it is thought to represent a normal extracellular transudate [12,13]. Goodson calculated the turnover rate of gingival fluid to be 40 times per hour and suggested that this accounts for the rapid clearance and short duration of action observed with irrigation treatment [14].

The periodontal pocket provides a natural reservoir, which is easily accessible for the insertion of a delivery device. The GCF provides a leaching medium for the release of a drug from the dosage form and for its distribution throughout the pocket. These features, together with the fact that the periodontal diseases are localised to the immediate environment of the pocket, make the periodontal pocket a natural site for treatment with local delivery systems. The diagrammatic representation of application of various intra-pocket delivery devices in the periodontal pocket is shown in Fig. 3.

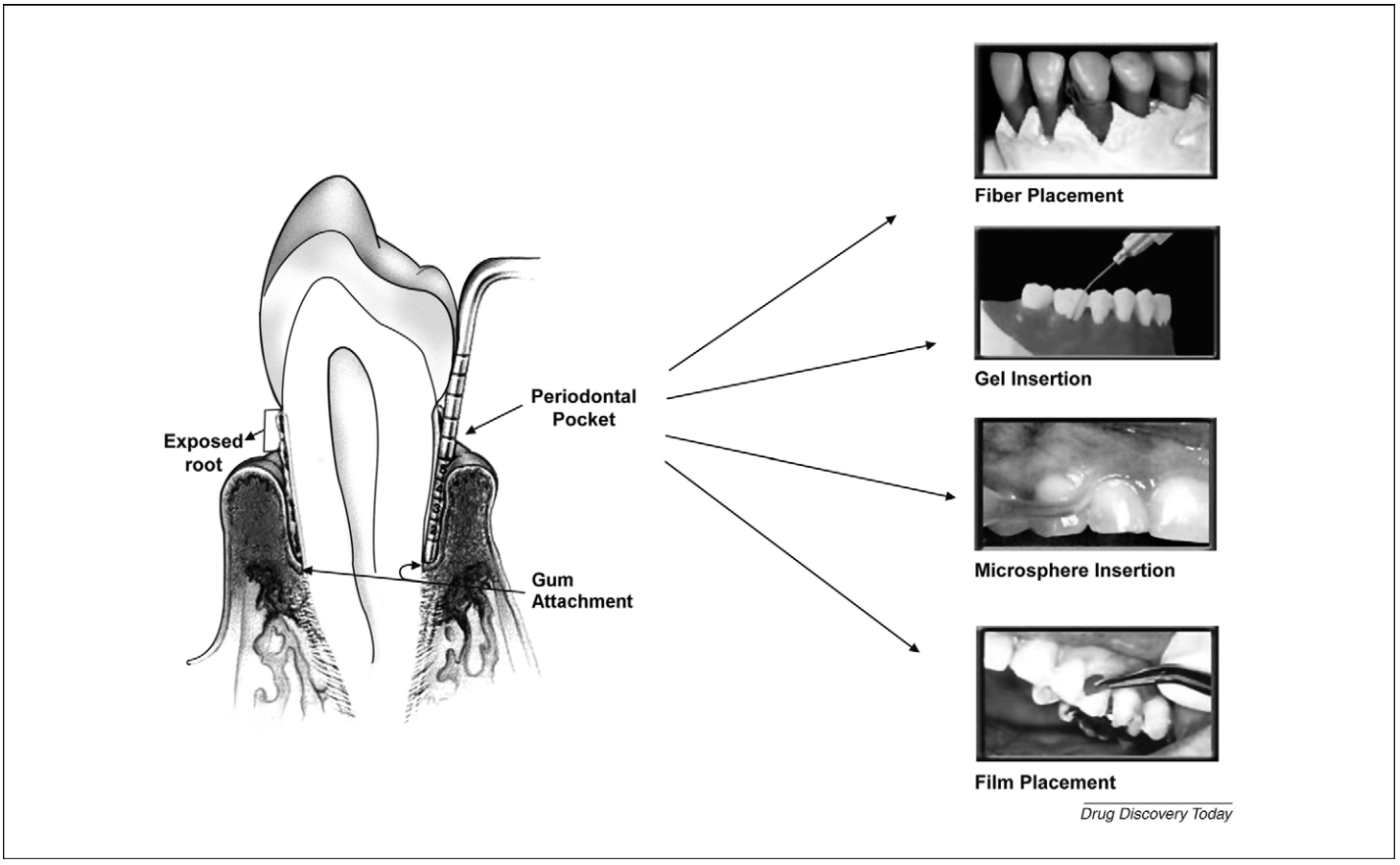

FIGURE 3

Diagrammatic representation of application of various intra-pocket delivery devices. Fibre packed under gum; gel injected into periodontal pocket; microspheres expelled under gum; and film placement under gum.

TABLE 1

Summary of some investigated intra-pocket delivery systems

System	Polymer matrix	Drug Incorporated	Refs
Fibers	Cellulose acetate	Tetracycline HCl	[15]
		Chlorhexidine	[18]
	Ethylene vinyl acetate	Tetracycline HCl	[23]
	Poly(ε-caprolactone) (PCL)	Tetracycline HCl	[23]
Strip	Polyethylmetha acrylate (acrylic)	Tetracycline HCl	[25]
		Metronidazole	[26]
	Hydroxypropyl cellulose	Chlorhexidine, tetracycline	[28]
		Doxycycline	[29]
	Hydroxypropyl cellulose + methacrylic acid	Ofloxacin	[30,31]
	Polyhydroxybutyric acid	Tetracycline HCl	[32]
	Polylactide-co-glycolic acid (PLGA)	Tetracycline HCl	[33]
		Chlorhexidine	[34]
	Ethyl cellulose	Chlorhexidine	[36]
Films	Ethyl cellulose	Metronidazole	[42]
		Tetracycline HCl	[43]
		Minocycline	[44]
	Cross-linked atelocollagen	Tetracycline	[40]
	Gelatin (Byco® protein)	Chlorhexidine diacetate	[48]
	Cross-linked gelatin + glycerine	Chlorhexidine digluconate	[49]
	Chitosan	Taurine	[50]
	Chitosan + PLGA	Iproflavone	[51]
	Chitosan + PCL	Metronidazole	[52]
	Polyvinyl alcohol + carboxymethyl chitosan	Ornidazole	[53]
	PLGA	Tetracycline	[54]
		Amoxycillin + metronidazole	[56]
	Poly(*ortho* ester)	Metronidazole	[57]
	Eudragit L® and Eudragit S®	Clindamycin	[58]
	PCL	Minocycline	[59]
Gels	Chitosan	Metronidazole	[68]
	Hydroxyethyl cellulose + polyvinylpyrrolidone	Tetracycline	[69]
	Hydroxyethyl cellulose + polycarbophil	Metronidazole	[70]
	Poloxamer 407 + Carbopol 934P	Propolis	[71]
	Poly(DL-lactide) + *N*-methyl 2-pyrrolidone	Saguinarium	[72]
		Doxycycline hyclate	[73]
	Glycerol monooleate + sesame oil	Metronidazole	[74]
	PLGA	Tetracycline	[75]
Microparticles	Pluronic F 127	Tetracycline	[76]
	PLGA	Tetracycline	[77]
		Histatin peptides	[78]
	PLGA + PCL	Doxycycline	[79]
Nanoparticles	2-Hydroxyethyl methacrylate + polyethylene glycol dimethacrylate	–	[81]
	PLGA	*Harungana madagascariensis* leaf extract	[82]
	Chitosan	Antisense oligonucleotide	[84]
	Cellulose acetate phthalate	Triclosan	[85]
	PLGA	Triclosan	[85]
Vesicular system	Phosphatidylinositol	Triclosan	[88]
	Immunoliposomes	Anti-oralis	[90]
Other system	Poly(ethylene-co-vinyl acetate)	Acyclovir	[94]
		Chlorhexidine	[94]

Intra-pocket drug delivery systems are highly desirable due to the potentially lower incidence of undesirable side effects, improved efficacy and enhanced patient compliance. The attractiveness of treating periodontal diseases by the intra-pocket drug delivery systems is based on the prospects of maintaining effective high levels of drug in the GCF for a prolonged period of time to produce the desirable clinical benefits.

For these systems, the delivery vehicles can be of natural origin or semisynthetic or synthetic nature. Recent developments in polymer sciences have disclosed biocompatible and biodegradable synthetic polymers, which can be modified to meet pharmacological and biological requirements. Many polymer-based intra-pocket devices containing therapeutic agents for the treatment of periodontal disease have been studied and are listed in Table 1.

Drug delivery devices

Fibres

Fibres, or thread-like devices, are reservoir-type systems, placed circumferentially into the pockets with an applicator and secured

with cyanoacrylate adhesive for the sustained release of the entrapped drug into the periodontal pocket.

Hollow fibres made up of cellulose acetate filled with tetracycline hydrochloride were described by Goodson *et al.* [15]. When placed into the periodontal pocket these systems were effective in reducing pathogenic subgingival microorganisms and results were comparable, but slightly lower in magnitude, with those obtained by scaling and root planning [16]. The release of the tetracycline from the cellulose acetate fibres as occurred by diffusion mechanism is rapid with approximately 95% of the drug released in the first two hours and, therefore, a single application of these fibres does not provide an effective drug concentration for long periods [17]. Compared with the less effective tetracycline delivery from hollow fibres, fibres containing 20% (v/v) chlorhexidine, when placed into periodontal pockets, exhibited a prompt and marked reduction in signs and symptoms of periodontal disease [18].

In spite of the fact that the hollow fibres served as a good drug holding device, they permitted rapid evacuation of the drug. To retard drug release, drug-impregnated monolithic fibres were developed by adding drug to molten polymers, spinning at high temperature and subsequent cooling [19]. Several polymers such as poly(ε-caprolactone) (PCL), polyurethane, polypropylene, cellulose acetate propionate and ethyl vinyl acetate (EVA) have been investigated as matrices for the delivery of drug to the periodontal pocket. In this respect, monolithic EVA fibres were found to be effective in controlling the release of encapsulated drug, and the same has been demonstrated by several *in vitro* and *in vivo* studies [7,20–22]. Tonetti *et al.* reported that EVA fibres containing 25% tetracycline hydrochloride maintained a constant drug level in the GCF above 600 μg/ml throughout ten days, showing zero-order release characteristics of EVA fibres [23]. In addition to the extensive evaluation of drug delivery kinetics from the EVA fibres, this system has undergone numerous clinical trials to test its efficacy in the treatment of periodontal diseases. A study conducted on 121 sites in 20 patients evaluated the safety and efficacy of tetracycline-loaded EVA fibres applied after scaling and root planning (SRP) for ten days. The study indicated that a significant reduction in probing depth and gain in attachment was present at one-, three- and six-month visits. A reduction in proportion of bleeding pockets was observed during the experimental period [7].

Tetracycline fibre treatment adjunctive to SRP showed significantly less periodontal disease recurrence (4%) compared with SRP alone (9%), tetracycline fibre alone for 10 days (10%) and tetracycline fibre alone for 20 days (12%) [24]. Studies that were well-conducted and well-controlled have demonstrated the clinical efficacy of these fibres but their actual value in patient therapy has been somewhat difficult to interpret because clinicians have found the fibre placement technique challenging. A study showed that patients experienced discomfort during fibre placement and at fibre removal various degrees of gingival redness were observed [7]. The intricacies of winding a fibre into place, the need to retain the device within the pocket and then the removal of it after seven to ten days may limit its wide acceptance by patients and periodontists [21].

Strips

Strips are thin and elongated matrix bands in which drugs are distributed throughout the polymer. Generally, strips are made up of flexible polymers having a position securing mechanism, and accommodate a wide range of interproximal spacing. Acrylic (polyethyl methacrylate) strips loaded with various antimicrobial agents have been developed and evaluated [25,26]. Strips containing tetracycline or metronidazole were found to be effective in producing changes in the subgingival flora and improving the clinical parameters of periodontal disease [25]. The same author reported that metronidazole-loaded acrylic strips achieved clinical effects similar to conventional mechanical therapy and this effect was greater than that produced by chlorhexidine- or tetracycline-loaded acrylic strips [26]. Treatment with metronidazole-loaded fibres or SRP was also associated with a slower rate of relapse of clinical parameters. The change in physical properties of acrylic strips in the serum has been reported [27]. These strips dissolved slightly in serum, softened and were difficult to remove, leading to the risk of leaving injurious acrylic material in the periodontal pocket, which may evoke an inflammatory reaction [27]. A strip that slowly erodes inside pocket is an ideal method to obviate the disadvantages mentioned above. Many biodegradable devices in the form of a strip have been fabricated and evaluated. The earliest reported bioabsorbable strips were based on hydroxypropyl cellulose for the delivery of chlorhexidine [28], tetracycline [28] and doxycycline [29]. The study by Noguchi *et al.* demonstrated a rapid *in vitro* release of drugs from the strips within two hours with maximum dissolution of the strip occurring after three hours. Chlorhexidine-loaded strips showed reduction in probing depths, plaque index, gingival index and rate of bleeding on probing. In treated sites, the decreased proportions of *Bacteroides asaceharolyticus* were also observed [28]. Although this was a pioneering study in the development of biodegradable systems, the fast degradation of the system and rapid release of the drug were distinct disadvantages. The hydroxypropyl cellulose strips were modified by incorporating soluble methacrylic acid co-polymer particles to form a controlled release strip (PT-01) [30]. A single application of PT-01 in the periodontal pocket maintained ofloxacin concentration higher than the minimum inhibitory concentration of most periodontopathic bacteria in GCF for over seven days [30]. Weekly application of PT-01 for two weeks showed reduction in proportions of spirochetes and motile rods whilst coccoid cell increased. Although the weekly application of PT-01 for four weeks showed statistically no significant differences in the microbiological results between the strip group and the SRP group. Consequently, the authors suggested that the application of PT-01 as an adjunct in conventional periodontal therapy would be able to provide beneficial effects [31].

Different types of synthetic biodegradable polymers such as polyhydroxybutyric acid (PHBA) and polylactide co-glycolic acid (PLGA) have been evaluated as a matrix for sustained delivery of tetracycline. PHBA strips containing 25% tetracycline showed sustained release over four to five days with a significant burst effect at day 1 [32], whereas, PLGA strips containing 25% tetracycline (25 TTC–PLGA) released therapeutic concentrations of the drug for ten days [33]. Application of intracrevicular 25 TTC–PLGA, when compared to SRP, showed enhanced antibacterial effect and a similar clinical effect in supportive periodontal therapy patients [33]. Recently, the results of the multicentre clinical trials have demonstrated that the adjunctive use of the PLGA chlorhexidine chip resulted in a greater reduction of periodontal pocket depth and additional gain in clinical attachment level compared to SRP alone [34]. These results were concomitant with

those obtained by a randomised, controlled single-blinded trial using the same system [35]. The most interesting and long-term clinical improvement was demonstrated by controlled release of ethyl cellulose strips containing chlorhexidine [36]. The *in vitro* release of niridazole from ethyl cellulose inserts was steady and sustained for over seven days and the inserts also demonstrated a significant improvement in clinical indices. Significant reduction in total bacterial count in GCF was observed pre- and post-device insertion, as well as between control and treatment groups [37]. Several bioabsorbable dental materials like haemostatic gauze made of oxidised regenerated cellulose (Surgicel®), a collagen wound dressing (CollaCote®) and a fibrin sealant (Tissel®) have been investigated by Larsen *et al.* for their potential use as carrier materials for doxycycline [27]. Surgicel® produced a relatively higher antibacterial activity compared to intermediate for Tissel® and lower for CollaCote® [27].

In the field of herbal drug delivery, recently, green tea catechin showed a bactericidal effect against *Porphyromonas gingivalis* and *Prevotella* sp. *in vitro* with an MIC of 1.0 mg/ml. The application of green tea catechin through an intra-pocket delivery system using slow release cellulose strips was effective in improving the periodontal status [38]. So far, no product has been marketed because of the non-biodegradable nature of the polymeric carriers or only temporary clinical improvements after treatment completion.

Films

A far more widely used form of intra-pocket delivery device has been in the shape of film, prepared either by solvent casting or direct milling. Bigger films either could be applied within the cavity onto the cheek mucosa or gingival surface or could be cut or punched into appropriate sizes so as to be inserted into the site of action. Films are matrix delivery systems in which drugs are distributed throughout the polymer and release occurs by drug diffusion and/or matrix dissolution or erosion. This dosage form has several advantageous physical properties for intra-pocket use [39]. The dimensions and shape of the films can be easily controlled according to the dimensions of the pocket to be treated. It can be rapidly inserted into the base of the pocket with minimal discomfort to the patient. If the thickness of the film does not exceed 400 μm, and it has sufficient adhesiveness, it will remain submerged without any noticeable interference with the patient's oral hygiene habits. Films that release drugs by diffusion alone are prepared using water-insoluble non-degradable polymers [13,25], whereas those that release by diffusion and matrix erosion or dissolution use soluble or biodegradable polymers [40,41].

Non-biodegradable ethyl cellulose based films for the delivery of chlorhexidine diacetate [36], metronidazole [42], tetracycline [43] and minocycline [44] have been developed by solvent evaporation method and clinically tested. Ethyl cellulose films showed sustained drug release and release rates were dependent on the casting solvent and drug load. The use of chloroform as the casting solvent significantly retarded the release rate of the drug compared to ethanol as the casting solvent. The incorporation of polyethylene glycol in the films, however, enhanced the release rate of the drugs [42].

Published clinical findings also confirmed that the treatment with drug-loaded ethyl cellulose films produced significantly greater improvements in the incidence of bleeding on probing, probing depths and attachment levels when compared to the conventional maintenance treatment [45–47]. In contrast to the non-degradable systems discussed above, the films made up of degradable polymers erode or dissolve in the gingival crevice so that removal after treatment is not required. Natural and synthetic biopolymers play a pivotal part in drug delivery to periodontal pocket. Amongst natural biopolymers, atelocollagen, a pepsin-digested preparation of insoluble bovine skin collagen, has been investigated as a possible carrier material for antibacterial agents in periodontal disease [40,48]. Prolonged concentration of tetracycline in GCF could be maintained for at least ten days by incorporating the drug in glutaraldehyde cross-linked atelocollagen. Application of these films resulted in a significant improvement in clinical parameters [40]. Another natural polymer, gelatin (Byco® protein), obtained from fish, was cross-linked and used as a sustained release device for the delivery of chlorhexidine diacetate or chlorhexidine hydrochloride [48]. *In vitro* drug release from such degradable films varied from 4 to 80 hours, depending on the amount of drug and cross-link density of the polymer.

More recently, a film composed of cross-linked hydrolysed gelatin and glycerine for local delivery of chlorhexidine digluconate has been developed and commercialised under the tradename Periochip® [49]. The system showed an initial burst effect, whereby 40% of chlorhexidine was released in the first 24 hours, followed by a constant slower release over about seven days. This film has the advantage over other biodegradable films in which it remains inside the pocket with no additional aids for retention because of the adhesive nature of the Periochip® components [49].

The novel natural polymer chitosan is also utilised as a polymeric matrix in the form of film enriched with taurine (antioxidant agent). Taurine enhances the wound healing ability of chitosan and could be considered beneficial in tissue repair in destructive diseases like periodontitis [50]. Furthermore, Perugini *et al.* carried the periodontal delivery of ipriflavone in a new chitosan/PLGA film delivery system [51]. Monolayer films made of ipriflavone-loaded PLGA micromatrices in a chitosan film were compared with multilayer films composed of chitosan/PLGA/chitosan (three layers). *In vitro* experiments demonstrated that the composite micromatricial films represent a suitable dosage form to prolong ipriflavone release for 20 days [51]. In another study, a two-layered film utilising mucoadhesive chitosan and biodegradable PCL was prepared. The film containing chitosan:PCL in the ratio of 1:0.625 had the best tensile properties and the slowest metronidazole release rate. *In vivo* evaluation of this film revealed that metronidazole concentration in saliva over six hours ranged from 5 to 15 μg/ml, which was within (and at the top end higher than) the reported range of minimum inhibitory concentration for metronidazole. A significant *in vitro*:*in vivo* correlation under the adopted experimental conditions was also obtained [52]. The distinguishable films composed of poly(vinyl alcohol) (PVA) and carboxymethyl-chitosan (CMCS) were prepared by blending/casting methods, and loaded with ornidazole as a periodontal drug delivery system. The blended films were found to be biocompatible, showed pH-responsive swelling, had a good retention at the application site and maintained high drug concentration at least for five days [53].

Synthetic biodegradable polymers have also been evaluated for sustained release of drug in the periodontal pocket [54–56]. The combination of amoxycillin and metronidazole in the carrier

polymer PLGA showed not only an extended spectrum of antimicrobial activity but also a synergistic effect against *E. limosum*, which had been reported to be resistant to metronidazole in earlier studies [56]. The films showed a sustained *in vitro* release for a period of 16 days and the *in vivo* drug concentrations were maintained above the MIC value for the entire period of the release studies. By contrast, PLGA films containing tetracycline hydrochloride [54,55] showed poor retention in the periodontal pockets with incomplete release of tetracycline. This effect could be attributed to the hydrophobic nature of PLGA matrix and the difference in physicochemical properties of the drugs. Another biodegradable polymer poly(*ortho* esters) was also explored for the controlled delivery of metronidazole [57]; however, no study on patients has been reported.

Higashi *et al.* prepared films of water-soluble polymer Eudragit S® and non-water-soluble polymer Eudragit L® for the delivery of clindamycin. An *in vitro* release study showed that insoluble films release drug by diffusion and soluble films release drug by dissolution of the carrier [58].

Kyun and co-workers showed that by embedding minocycline in PCL it is feasible to obtain sustained release of the drug within the periodontal pocket for seven days and should be a useful tool for the elimination of pathogenic microflora from periodontal pocket or reducing inflammation in periodontal disease [59]. Dedein *et al.* performed a clinico-laboratory study for the treatment of periodontal diseases using chlorhexidine-loaded Diplen-Denta films. The new treatment was found to be highly effective in patients with catarrhal gingivitis and generalised periodontitis of light and medium severity [60].

Injectable gels

Together with the solid devices, semisolid formulations also receive reasonable attention for the localised delivery of antibiotics [61]. Semisolid or gel formulations can indeed have some advantages. In spite of the relatively faster release of the incorporated drug, gels can be more easily prepared and administered. Moreover, they possess a higher biocompatibility and bioadhesivity, allowing adhesion to the mucosa in the dental pocket and, finally, they can be rapidly eliminated through normal catabolic pathways, decreasing the risk of irritative or allergic host reactions at the application site.

Various oleogels and hydrogels for the delivery of tetracycline (2.5%), metronidazole (25%), metronidazole benzoate (40%), as well as a combination of tetracycline (2.5%) and metronidazole benzoate (40%), have been tested and satisfactory results have been achieved. The gels composed of cellulose derivatives such as hydroxypropylmethyl cellulose [62] and hydroxyethyl cellulose [63–65] do not appear to have sustained release properties. Surprisingly, despite the rapid drug release and poor retention of these gels, positive clinical results in moderate to deep periodontitis were obtained.

Bioadhesion or mucoadhesion is a preliminary requirement for prolonged release of the drug at the site [66]. The retention time, as determined by fluorescein release, was found to be significantly higher for chitosan gel as compared to xanthan gum and poly(-ethylene oxide) gel [67]. Chitosan, a novel biodegradable natural polymer, in a gel form (1%, w/w) with or without 15% metronidazole, had demonstrated effectiveness in the treatment of chronic periodontitis [68]. Bioadhesive semisolid, polymeric system can be utilised as an important intra-pocket delivery vehicle because it can easily pass through a cannula into a periodontal pocket where it solidifies *in situ* to deliver the therapeutic agent for a prolonged period. These systems exhibit a pseudoplastic flow and thermoresponsive behaviour, existing as a liquid at room temperature and gel at 34–37 °C.

Tetracycline-loaded bioadhesive semisolid, polymeric system based upon hydroxyethyl cellulose- and polyvinylpyrrolidone- [69] and metronidazole-loaded systems based upon Carbopol 974P, hydroxyethyl cellulose and polycarbophil [70] are reported. Another such system composed of Poloxamer 407 and Carbopol 934P and containing propolis extract were designed for the treatment of periodontal disease [71]. The release of the propolis was controlled by the relaxation of polymer chains and the greatest mucoadhesion was noted for the formulation containing 60:1 ratio of Poloxamer 407:Carbopol 934P [71].

Another injectable biodegradable gel based on poly(DL-lactide) dissolved in a biocompatible solvent *N*-methyl-2-pyrrolidone (NMP) (Atrigel®) was widely studied [72,73]. The Atrigel® loaded with 10% doxycycline hyclate showed high levels of doxycycline (250 μg/ml) in the GCF for a period of seven days. Interestingly, levels of 10–20 μg/ml were still present for three to five days after the polymer had been removed [73]. It is possibly because of minute particles of polymer remaining within the pockets or because of the substantive effects of tetracyclines within the periodontal pocket-adjacent-tooth-surface environment. In another study, Atrigel® containing 5% sanguinarine was found to be superior to the control in the treatment of adult periodontitis and the findings have been recently confirmed in a human clinical trial [72].

The semisolid system based on water-free mixtures of lipids, such as glycerol monooleate (monoglyceride) and sesame oil (triglyceride), is characterised by a solid–gel transition and become semisolid on contact with gingival fluid in the periodontal pocket. The system is based on the ability of glycerides to form liquid crystals, that is, reverse hexagonals on contact with water. The reverse hexagonal form has more favourable sustained release properties, compared with the initial cubic form. The matrix is degraded by neutrophils and bacterial lipase in the GCF [74].

Biodegradable gels are other useful prospects for the delivery of therapeutic agents into periodontal pockets. Bioerodible lactic–glycolic acid gels were found to be safe and tetracycline levels observed at days 3 and 8 probably represent significant antimicrobial efficacy [75].

Microparticulate system

Non-biodegradable as well as biodegradable materials have been investigated for the preparation of microspheres. These materials include the polymers of natural origin, modified natural substances and synthetic polymers. They could preferably be formulated as a chip or could be part of a dental paste formulation, or otherwise be directly injected into the periodontal cavity. Tetracycline-containing microcapsules in Pluronic F127 were reported to form gel at body temperature and hold the microcapsules in the periodontal pocket for the duration of treatment [76]. PLGA microcapsules and microspheres have been proposed for the delivery of tetracycline [77] and histatins [78]. These microparticulate systems provide stability to

the encapsulated drug [78]. The *in vitro* drug release from such systems depends upon the polymer (lactide:glycolide) ratio, molecular weight, crystallinity and pH of the medium. Some questions, however, related to the retention of such formulations in the periodontal pocket need clarification. Recently, the controlled delivery of doxycycline for up to 11 days was achieved through novel biodegradable microspheres prepared by w/o/w double emulsion technique using the blends of PLGA and PCL in different ratios. The formulation was also effective *in vivo* and significant results were obtained with respect to microbiological and clinical parameters for up to three months [79].

Nanoparticulate system

Modern drug delivery systems are designed for targeted controlled slow drug release. Up to now polymer or microparticle-based hydrogels have been applied in dentistry, which can affect the rate of release because of their structure. Recently, intensive research is being performed all over the world to improve the effectiveness of delivery systems. The nanoparticulate system provides several advantages as compared with microspheres, microparticles and emulsion-based delivery systems, including high dispersibility in an aqueous medium, controlled release rate and increased stability. Nanoparticles, owing to their small size, penetrate regions that may be inaccessible to other delivery systems, such as the periodontal pocket areas below the gum line. These systems reduce the frequency of administration and further provide a uniform distribution of the active agent over an extended period of time [80].

Biocompatible nanoparticles composed of 2-hydroxyethyl methacrylate (HEMA) and polyethyleneglycol dimethacrylate (PEGDMA) could be used as a drug delivery system for dental applications. The polymer-based nanoparticles were prepared via micellar polymerisation, which resulted in a well dispersible white powder material with particle size in the range of 50–180 nm. These nanoparticles are suitable for incorporation into a hydrogel matrix and to design new drug delivery devices for dental applications [81].

Moulari *et al.* investigated the *in vitro* bactericidal activity of the *Harungana madagascariensis* leaf extract (HLE) on the oral bacterial strains largely implicated in dental caries and gingivitis infections. HLE-loaded PLGA nanoparticles were prepared using interfacial polymer deposition following the solvent diffusion method. Incorporation of the HLE into a colloidal carrier improved its antibacterial performance and diminution of the bactericidal concentration was observed [82].

Shefer and Shefer patented a controlled release system useful for site-specific delivery of biologically active ingredients over an extended period of time. This system is a multi-component release system comprising biodegradable nanoparticles having bioadhesive properties encapsulated within a moisture sensitive microparticle. The bioadhesive properties of the nanoparticles are attributed to the positively charged surfactant entrapped on the particle surface. The multi-component release system can be incorporated into any suitable oral hygiene product including gels, chewing gums, toothpaste and mouthwash for the treatment and prevention of periodontal disease [83]. Antisense oligonucleotide-loaded chitosan-tripolyphosphate (TPP) nanoparticles were prepared and evaluated. Chitosan/oligonucleotide-TPP nanoparticles, which were prepared by adding TPP after the formation of chitosan/oligonucleotide complex, showed the sustained release of oligonucleotides and are suitable for the local therapeutic application in periodontal diseases [84].

In an attempt to obtain a novel delivery system adequate for the treatment of periodontal disease, triclosan-loaded polymeric (PLGA, PLA and cellulose acetate phthalate) nanoparticles were prepared by emulsification–diffusion process. A preliminary *in vivo* study in dogs with induced periodontal defects suggested that triclosan-loaded nanoparticles penetrate through the junctional epithelium [85].

With the emergence and increase of microbial resistance to multiple antibiotics, the antibiotic-free delivery systems for periodontal infections have been tried. The problem of antibiotic resistance has led to resurgence in the use of Ag-based antiseptics that may be linked to broad-spectrum activity and far lower propensity to induce microbial resistance than antibiotics [86]. Ag nanoparticles can be used as effective growth inhibitors in various microorganisms, making them applicable to treat periodontal diseases. Another approach is antimicrobial enzymes covalently attached to nanoparticles to generate antibiotic-free treatment for microbial infections. Satishkumar *et al.* developed a system in which hen-egg lysozyme (antimicrobial enzyme) was covalently attached to two types of polystyrene latex nanoparticles: positively charged, containing aliphatic amines surface group; and negatively charged, containing sulphate and chloromethyl surface group. These particles were showing lower activity compared to free enzyme, but can be explored for targeted antimicrobial activity [87].

Vesicular system

Vesicular liposomal systems are designed to mimic the bio-membranes in terms of structure and bio-behaviour, and hence are investigated intensively for targeting periodontal biofilms. Jones and Kaszuba reported interactions between liposomes made up of phosphatidylinositol (PI) and bacterial biofilms. The targeting of liposomes was thought to be because of the interaction of the polyhydroxy groups of liposomes with surface polymers of the bacterial glycol-calyx [88].

Succinylated Concanavalin-A (lectin)-bearing liposomes (proteoliposomes) have been found to be effective for the delivery of triclosan to periodontal biofilms. *In vitro* and *in vivo* studies have revealed that, even after a very short exposure, the proteoliposomes are retained by the bacteria eventually delivering triclosan into the cellular interiors. The potential of lectin-bearing liposome systems as a targeting system for the control of gingivitis and dental plaque has been extensively studied by Vyas *et al.* [89].

The delivery of triclosan and chlorhexidine was studied for several liposomal compositions involving cationic as well as anionic lipids [90]. Robinson and co-workers reported further on the affinity and specificity of immunoliposomes to reduce dental plaque. The anti-oralis immunoliposomes showed the greatest affinity for *S. oralis* and affinity was unaffected by net charge on the lipid bilayer or by the number of antibodies conjugated to the liposomal surface [91].

Miscellaneous: low-dose antibiotic

Recently, there has been interest in the use of low-dose antibiotics. The dose is so low that the drug does not act to kill bacteria, but

rather to change the way the body responds to infection. Production of the enzyme collagenase is essential because older gingival tissues are replaced with new tissues. In periodontal disease there is an overproduction of collagenase, causing the destruction of healthy gum tissue. An interesting effect of low-dose antibiotics is that they not only kill the bacteria that may cause periodontal disease but also reduce the body's production of collagenase, an enzyme that destroys gingival tissues. The antibiotic doxycycline was found to combat these enzymes, even in doses so small that there was no antibiotic effect [92]. The advantages of smaller doses are that there is a great reduction in the chances of formation of resistant bacterial strains and side effects. Periostat is a capsule of 20 mg of doxycycline, and clinical studies have shown that patients who take two capsules daily have a reduction in clinical inflammation [93]. The daily 40-mg dose is so low as not to qualify as an antibiotic, and there is no known effect on the pocket bacteria. Thus, Periostat must be used in conjunction with other therapies that address bacterial removal.

Current status of intra-pocket delivery devices in periodontics

With the current availability of number of intra-pocket delivery systems containing antimicrobials for periodontal therapy, questions can be raised about the role of intra-pocket delivery devices in periodontics. Firstly, if intra-pocket delivery systems can deliver equivalent clinical results to SRP, should the use of these therapies be considered in place of SRP? Better still, how will antimicrobials be incorporated into treatment strategies with or without mechanical intervention? Lastly, to be considered are the physical properties of delivery system, which may influence the acceptance by the patient and professional community. Most reports on the local delivery concepts have appeared in the periodontal literature but there are surprisingly few studies that demonstrate the clinical efficacy using intra-pocket delivery systems in periodontitis patients. Despite the large number of studies, there are insufficient comparative data to support any one of the local delivery systems as superior to another because their treatment patterns differ widely. 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.

Many studies have failed to show real and clinically meaningful effects provided by the intra-pocket drug delivery systems when used as stand-alone monotherapies. Other studies have demonstrated that these systems have beneficial effects in terms of probing depth reduction; however, the statistical significance reached in these studies was not always clinically significant.

TABLE 2

The strategic approaches with associated challenges and achievements towards the formation of periodontal drug delivery system

Challenges		Goals achieved
Strategy 1: systemic delivery devices		
1	Low benefit to risk ratio, ingestion of large drug doses	
2	Inadequate drug concentration at periodontal site	
3	Rapid/non-sustained drug release	
4	Poor patient compliance: frequent administration	
5	No penetration of delivery system	
6	No adhesion/retention into periodontal pocket	
7	High incidence of bacterial resistance	
Strategy 2: local mouth rinses and dental irrigation		
1	Inadequate drug concentration at periodontal site	Drug dose is reduced
2	Rapid/non-sustained drug release	Systemic toxicity is decreased
3	Poor patient compliance: frequent administration	
4	No penetration of delivery system	
5	No adhesion/retention into periodontal pocket	
6	High incidence of bacterial resistance	
Strategy 3: non-biodegradable, intrapocket fibres, strips, films and microparticles		
1	Poor patient compliance: discomfort during the placement of device, at least two visits to therapist is required and development of foreign body response, if left *in situ*	Adequate drug concentration at periodontal site
2	Poor penetration of system/drug	Prolonged/sustain drug release
3	Poor retention of system into periodontal pocket	Less frequent administration
4	Low incidence of bacterial resistance	
Strategy 4: biodegradable, intra-pocket fibres, strips, films and microparticles		
1	Poor patient compliance: discomfort during placement	Visit to therapist is reduced
2	Poor penetration of system/drug	No foreign body response
3	Poor retention of system into periodontal pocket	
4	Low incidence of bacterial resistance	
Strategy 5: biodegradable nanoparticles		
1	Poor retention of system into periodontal pocket	Placement is easier
2	Low incidence of bacterial resistance	Good penetration due to nano-sized particles
Strategy 6: mucoadhesive, biodegradable nanoparticles		
1	Low incidence of bacterial resistance	Good retention of system
Strategy 7: antibiotic-free, mucoadhesive, biodegradable nanoparticles		
		Bacterial resistance does not develop

TABLE 3

Criteria for the selection of optimal formulation parameters for developing periodontal drug delivery system

Disease site	Preferred drug	Preferred design	Preferred device
Local environment of the pocket	Cationic drug that adsorbs to surface of soft tissue wall, for example, chlorhexidine	Mucoadhesive Biodegradable Controlled release	Gels Fibres, strips, films Microparticles
Gingival tissues or deep seated infections	Strong chelating agents that attached to calcified hard tissues and penetrate into soft tissues, for example, tetracycline	Mucoadhesive Biodegradable Controlled release	Nanoparticles Coated nanoparticles
	Absorbs rapidly from pocket into gingival tissues, for example, metronidazole, NSAIDs	Nanosize	

The adjuvant use of intra-pocket delivery devices with SRP produced more favourable outcomes. In particular, the controlled delivery devices are a useful adjunct to conventional surgical or non-surgical treatments, but are not the substitute for these measures.

Future strategic approaches

Although the attention towards treating bacterial infections has yielded many successful delivery devices, concerted efforts in developing ideal intra-pocket periodontal systems are still needed. Currently available formulations suffer from several disadvantages including: requirement of mechanical bonding of delivery system to a tooth surface, requirement for the removal of non-biodegradable delivery systems, lack of penetration into deeper regions of periodontal pocket and poor patient compliance.

To improve the usefulness of intra-pocket delivery systems, the aims of treatment with antibacterial agents must be clearly defined. Treatment for one to three days appears to be sufficient to alleviate the signs and symptoms of periodontal disease, but not to prevent recolonisation and reoccurrence of the condition. It may be that the most effective treatment is achieved with a combination of delivery systems. Initial treatment with a short-acting biodegradable system may be useful to provide a bactericidal concentration of the antibacterial agent within the periodontal pocket. Subsequent prolonged delivery of antibacterial agents to the area surrounding the pocket opening may then prevent pocket recolonisation from the oral cavity by the suppression of marginal plaque.

A prerequisite for drug delivery systems for localised periodontal therapy is, therefore, retention on the mucosal surface and controlled drug release at the site of action. A prolonged retention at the mucosal surface, using bioadhesive or mucoadhesive polymers, provides intimate contact between the dosage form and absorbing tissues that result in an increased retention time of the system in the periodontal pocket. Maximising the bioadhesive forces of systems, therefore, remains a significant goal in the developmental phase of long-retentive drug delivery systems. In addition to bioadhesivity, controlling the release of a drug from the dosage form is also desirable. Controlled drug delivery systems should provide a continuous delivery of drugs at predictable and reproducible kinetics for a predetermined period. The potential advantages of this concept include the minimisation of drug-related side effects and improved patient compliance. Furthermore, nanoparticles have unusual properties that can be exploited to improve periodontal drug delivery. Nanoparticles, because of their small size, have been found to penetrate pocket areas below the gum line that may be inaccessible to other delivery systems.

Therefore, a nanoparticulate system of biodegradable polymer coated with mucoadhesive polymer with biodegradability, controlled drug release, good retention in and around the periodontal pocket, ease of delivery and good penetration is a desirable approach for periodontal drug delivery. The strategic approaches with associated challenges and achievements towards the formation of a clinically effective, commercially feasible, physiologically acceptable intra-pocket-targeted drug delivery system is described in Table 2, whereas criteria for the selection of delivery system are represented in Table 3.

Parallel research in other fields, such as (a) the low-dose and chemically modified antibiotics, which act as inhibitors of collagenase, (b) the use of NSAIDs, which block the inflammatory pathway involved in periodontal tissue destruction, (c) the use of antimicrobial enzyme linked nanoparticles, which act as an antibiotic-free approach to treat infection and (d) the use of nano-injectable composite biomaterials in the form of cement, hold interest to enter a challenging new phase in dental research. Ultimately, the development of effective treatments will depend upon the work that combines molecular understanding of the disease and the success of delivery systems in the complex biological environment.

Conclusion

With a constant unravelling of molecular mechanisms, bacterial metabolism and pathogenesis behind periodontal infections, a paradigm shift from systemic antibiotics to intra-pocket-targeted delivery systems in dental pharmacotherapy is visible. A continued understanding of planktonic biofilm formation and bacterial adaptation to various antibiotics has further strengthened the choice of intra-pocket systems. Furthermore, with evidence of a large number of clinical studies of locally effective systems resulting in positive outcomes in terms of overall dental health, there is an inclination amongst dental practitioners to stop the empirical use of systemic antibiotics for the treatment of common dental afflictions. This development definitely paves the way for future patenting of novel, commercially feasible and physiologically acceptable intra-pocket-targeted drug delivery systems.

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