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Review

Sustained-Release Delivery Systems for Treatment of Dental Diseases

Michael Friedman[1,2] and Doron Steinberg[1]

Sustained-release delivery systems allow the effective targeting of drugs for treating dental and periodontal diseases. Since dental diseases are chronic, the therapeutic agents used should persist in the oral cavity for as long as possible. Implanting fluoride, chlorhexidine, and other antiseptic agents embedded into sustained-release polymeric matrices into the oral cavity prevents cariogenic plaque accumulation. Both fibers and slab-like sustained-delivery devices bearing chemotherapeutic agents reduced periopathogenic bacteria levels associated with clinical improvement. This review provides useful background information for researchers seeking to develop controlled-release delivery systems for dental applications.

KEY WORDS: caries; periodontal diseases; sustained release; local application; fluoride; chlorhexidine; tetracycline; metronidazole.

INTRODUCTION

Dental diseases are among the most widespread chronic disorders affecting mankind. The high incidence of caries and periodontal disease is borne out by epidemiological studies carried out in many parts of the world (1–3). Dental caries is prevalent mainly among the younger age groups, whereas periodontal disease is more common among the elderly. Compared to the widespread use of drugs for treating many medical conditons, relatively little use has been made of such forms of therapy in dental settings. Although employed to allay pain and anxiety, and with the exceptions of fluoride, drugs have not been extensively used for treating dental diseases. The reasons behind this apparent omission are of interest in the context of controlled-delivery approaches. The effectiveness of dental drugs has generally been evaluated only for conventional delivery modes. Diseases of the oral cavity can often be traced to body compartments adjoining, but outside, the mucosal layer. Systemic administration of drugs for treating dental conditions may be effective for pathogenic processes that have "crossed" the mucosal barrier. However, if the disease remains outside the range of the host's defense system, systemic therapy simply uses the body as an inefficient conduit for drug delivery, diluting the agent several thousand-fold before it reaches the site of the infection. More direct approaches such as mouth rinses may also fail to maintain therapeutic concentrations for sufficiently long periods to have any effect on the bacterial population.

Eliminating cariogenic and periopathogenic bacteria is the first step toward healing dental diseases, in addition to playing a major role in prophylaxis. Since these disorders are chronic, the duration of drug retention at the target site is critical in both prevention and therapy. Local sustained-release delivery systems extend the period during which the drug is present in the oral cavity, thereby enhancing therapeutic potential. At present, dental drug forms based on the principle of controlled delivery are not commercially available, although several products of this type are under clinical evaluation.

DENTAL CARIES

Dental caries is a microbial disease that destroys the teeth. Three major elements are involved in carious lesion formation: the teeth themselves, the microflora *Streptococcus mutans* and *Lactobacillus*, and carbohydrates. Tooth hard tissue decay is the result of the collusion of all these factors over a sufficiently long period (Fig. 1). Tooth decay is caused by the organic acids, mainly lactic acid, as well as acetic and formic aids, produced from the fermentable carbohydrates by action of the subflora in the supragingival plaque.

Caries may be prevented by measures directed toward the abovementioned elements: (i) fluorides, which increase tooth resistance; (ii) antiseptic agents and oral hygiene practices directed toward reducing cariogenic bacteria levels; (iii) curbing the amount of sugar in the diet; and (iv) limiting the periods during which these critical factors coexist.

Good oral hygiene is the main factor contributing toward dental caries prevention. However, other treatment is frequently required in order to enhance and maintain the effects of oral hygiene measures.

Fluoride, widely used as an anticariogenic agent, increases the resistance of the enamel to acid demineraliza-

[1] Department of Pharmacy, School of Pharmacy, Hebrew University, Jerusalem, P.O. Box 12065, Jerusalem, Israel.
[2] To whom correspondence should be addressed.

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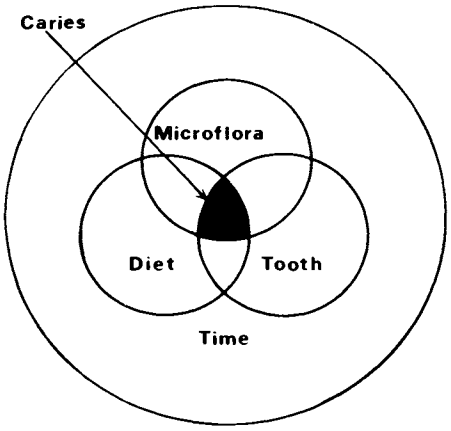

Fig. 1. Essential elements for carious lesion formation.

tion, remineralization, and antibacterial activity. Several fluoride salts are also employed in various toothpastes, tablets, drops, mouth rinses, and drinking water. The low retention time of fluoride in the oral cavity apparently constitutes the major disadvantage of all these fluoride delivery systems. Other problems with these vehicles include low patient compliance, poor drug targeting, difficulty in controlling dosage, toxicity, various adverse side effects, and social and legal controversies concerning their use.

Fluoridation is recommended only in areas with water fluoride levels below 1 ppm. Sustained-release dosage forms of fluoride were developed with the aim of increasing fluoride concentrations in the saliva to between 0.01 and 0.05 ppm, the levels found to occur in children living in areas with drinking water fluoride levels of 1 ppm.

Two general approaches were used to develop sustained-release applications for fluoride: (i) devices in which adhesives are used to mediate attachment of dosage forms to the tooth surface—pellet, microcapsules, or slabs; and (ii) self-adhesive vehicles such as varnishes. There are several significant differences between these two delivery forms. The first type has a relatively high loading capacity for fluoride, effectively creating a drug "reservoir" for long periods and, consequently, requiring a low frequency of application. On the other hand, varnishes, in contrast to pellets and microcapsules, are amenable to self-application without the assistance of a dentist or dental hygienist. The ability of varnishes to penetrate the tooth areas most vulnerable to caries, such as pits, fissures, interproximal contact areas, and crevices, is another advantage.

One controlled-release device for sodium fluoride, designed to undergo attachment to the tooth surface, is based on a copolymer hydrogel of hydroxyethyl methacrylate and methyl metacrylate. The inner core of the device serves as a reservoir of fluoride, while the outer layer, a copolymer of the same constituents at a different ratio, controls the drug release rates. The release of fluoride was found to be constant and linear—1.04 mg of fluoride was released daily during a 140-day period (4). Clinical trials carried out with a similar device revealed elevated fluoride levels in the dental plaque as well as in saliva (5). Rats fitted with such devices containing fluoride developed fewer carious enamel lesions compared to contols (6). Fewer carious lesions were also found in such rats than in those with subcutaneously implanted minipumps releasing fluoride at a similar rate (7). Friedman developed a controlled-release device for fluoride based on ethylcellulose or sililcone matrices (9,10). In *in vitro* studies, polymer films of this type were shown to release fluoride at rates of between 0.06 and 0.5 mg/day for up to 304 days. Ethylcellulose varnishes containing fluoride have been applied as coatings on orthodontic bands and chewing gums, and their use for intraoral delivery has been proposed. Elevated fluoride saliva levels were found following the application of 10% sodium fluoride in an ethylcellulose varnish, to the orthodontic plates in a group of children (11).

Several antibacterial agents were shown to display anticariogenic activity. However, prolonged use of systemic antibacterial agents gives rise to undesirable side effects. Mouth rinses, such as chlorhexidine and cetylpyridinium chloride, control dental plaque accumulation, but maximal effectiveness is achieved only if they are given daily. Some mouth rinses have a bitter taste and stain the teeth. For these reasons, patient compliance with mouth rinses is generally low.

Several approaches for controlled drug release aimed at achieving constant levels of antiseptic agents in the oral cavity have been probed. Polymeric varnishes as a vehicle for sustained delivery of antiseptic drugs preventing dental plaque formation is the most widely studied approach. Friedman's group showed (12–15) that a single application of chlorhexidine or cetylpyridinium in a sustained-release ethylcellulose varnish prevented plaque formation for periods of between 3 and 14 days. Drugs in this delivery mode, which are amenable to self-administration, significantly decrease the levels of the caries pathogen *Streptococcus mutans,* without affecting other components of the oral flora. Clinical trials brought to light another advantage of this delivery form—the absence of tooth staining and bitter taste. Several delivery modes for varnishes were evaluated in clinical trials: (i) direct application to tooth surfaces (13,16) and (ii) coating of orthodontic appliances (14,15) and dentures (12). The total amount of chlorhexidine and cetylpyridinium used in controlled-release delivery systems was only 10% of that required in mouth washes. Sandham and co-workers (17,18) examined the effects of two possible polyurethane varnish overcoatings for the chlorhexidine sustained-release application. A significant decrease in *Strepococcus mutans* levels was observed in a clinical study using this system. The need for application by a dentist is a major disadvantage of the sustained-release antiseptic delivery system developed by Sandham (17).

Clearly, sustained-delivery devices can be used to introduce anticariogenic drugs into the oral cavity. However, the effects of drugs administered in this manner are generally only short term, requiring frequent applications to maintain efficacy.

PERIODONTAL DISEASES

Periodontal diseases are inflammatory conditions affecting the physiological structural organs supporting the teeth. The gingiva become detached from the tooth to form periodontal pockets, providing an ideal ecological niche for pro-

liferation of anaerobic bacteria such as spirochetes, capnocytophaga, and bacteriodes, thereby provoking a host response which may lead to local inflammation (see Fig. 2). The resulting tooth mobility is eventually reflected clinically in tooth loss.

Conventional periodontal therapy relies almost exclusively upon mechanical debridgement of tooth surfaces and root planing and scaling as antimicrobial measures. However, in view of the fact that the bacterial specificity in periodontal disease is known, devising treatment protocols employing systemic and/or local antimicrobial agents should be possible.

Systemically administered antibiotics have been shown to lead to improvements on both the clinical and the microbiological levels (19,20). However, it is preferable to avoid antibiotic intake over long periods, which would be required to control periodontal disease, a chronic condition.

Local delivery systems, such as mouth rinses, have been shown to be able to keep supragingival plaque and gingivitis under control (21,22). On the other hand, such rinses were not effective against periodontal disease involving pocket formation (23), presumably due to inadequate drug penetration. However, it is possible to enhance drug entry deep inside the periodontal pocket by irrigation with the aid of a syringe. The effects of continuous irrigation with chlorhexidine solution for 28 days persisted for a further 28 days after cessation of treatment (24,25). Tetracycline intrapocket irrigation administered every 2 days for a period of 2 weeks decreased both periopathogenic bacteria levels and mean gingival and plaque indices for 8 weeks (26).

SUSTAINED-RELEASE DELIVERY SYSTEMS

Periodontal pockets are conducive to treatment with local sustained-release systems. Such intrapocket devices are required to release therapeutic levels of agents in the pockets and maintain drug levels for a sufficiently long period.

The size and depth of periodontal pockets are important to consider when designing such intrapocket devices. Clearly, they have to be small since the average pocket depth is between 6 and 8 mm. Thus, the active agent in the device should display therapeutic effectiveness at low doses.

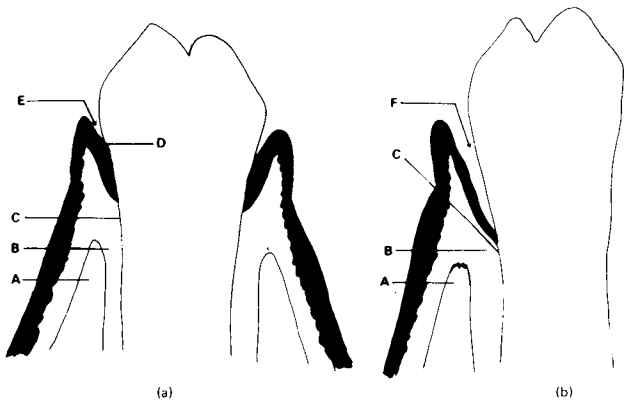

Fig. 2. (a) Healthy periodontium, (b) periodontal pocket, A = alveolar bone, B = periodontal ligaments, C = cementum, D = cementum-enamel junction, E = sulcus, F = periodontal pocket.

Delivery systems containing between 2 and 4 mg of the drug with release rates of several micrograms per hour, giving rise to therapeutically effective levels in the gingival fluid, are required (27,28).

In pilot studies, tetracycline-loaded hollow fibers (27) or chlorhexidine-ethylcellulose slabs (29) were introduced into the periodontal pockets for varying periods in order to determine the optimal duration of antibacterial activity in order to achieve long-term alteration of oral flora profiles. These studies suggested that treatment for up to 5 days was inadequate, whereas after 9 days of therapy, bacterial counts were below the detection level by dark-field microscopy.

The antibacterial drugs selected should be highly specific for the pathogenic bacteria in the pocket so as to prevent the development of resistant bacterial strains.

Data on the efficacies of four antibacterial agents against periodontal disease upon local application are presented in Table I. The drugs differ both with respect to mechanisms of action and physicochemical properties. Metronidazole specifically acts against anaerobic bacteria, and tetracycline and minocycline are effective against both aerobic and anaerobic bacteria, whereas chlorhexidine is an antiseptic agent with broad spectrum of activity. Tetracyclines and chlorhexidine are readily adsorbed by hard tissues, thereby increasing pocket drug levels and duration of action.

Clinical findings indicate that all these antibacterial drugs are effective for local treatment of periodontal disease. Comparing the clinical efficacies of these drugs in controlling the microbiological flora in periodontal pockets is important in view of their different microbial spectra and mechanisms of action.

Survival times of drug-bearing devices in the pockets play a key role in determining the outcome of the treatment. In addition, such devices have to be esthetically acceptable to the patient. In view of the vanity that most people exhibit regarding the mouth, such devices should not extend beyond the gingival margin, must not be bulky or interfere with normal daily oral hygiene, including toothbrushing and dental flossing, and should not require patients to change their dietary patterns. Since the inflamed periodontium is very sen-

Table I. Summary of the Properties of Sustained-Release Devices Containing Antibacterial Agents Used for Local Treatment of Periodontal Disease

		Effect of the treatment	
Active agent	Delivery system	Clinical parameters	% spirochetes
Tetracycline	Methacrylate/slab	Improvement	Reduced
Tetracycline	Ethylvinyl acetate/ fiber	Improvement	Reduced
Tetracycline	Ethylcellulose/slab	Improvement	Reduced
Minocycline	Ethylcellulose/slab	Improvement	Reduced
Metronidazole	Ethylcellulose/slab	Improvement	Reduced
Metronidazole	Ethylcellulose/slab	NA	NA
Chlorhexidine	Ethylcellulose/slab	Improvement	Reduced
Chlorhexidine	Protein/slab	Improvement	Reduced
Chlorhexidine	Hydroxypropyl cellulose/slab	Improvement	Reduced

sitive, the device should be amenable to rapid insertion into the pocket, and pain and discomfort to the patient during the 10-day treatment period should be minimized.

Goodson *et al.* (30) and Addy *et al.* (31) employed cyanoacrylates and periodontal packs, which are likely to cause inconvenience to the patient, to enhance device survival in periodontal pockets. The ethylcellulose device developed by Golomb *et al.* (28) exhibited good survival properties without the addition of periodontal packs—less than 2% of the 400 devices were lost during the course of the study. The film thickness in this device of only 0.2 mm, compared with 1 mm of the acrylic device of Addy *et al.* (31), resulted in excellent patient compliance and comfort. The adhesiveness of the biodegradable device developed by Steinberg *et al.* (32) assured 100% survival in periodontal pockets.

Fibers or slab-type pharmaceutical preparations, in either nondegradable or biodegradable forms, may serve as delivery systems (see Table I).

Addy *et al.* (31) proposed chlorhexidine gluconate loaded in a cellulose-based hollow-fiber device. Improvements in various parameters was recorded (33) in clinical trials. A hollow-fiber dialysis tube containing a solution of 0.5% metronidazole inserted in the periodontal pocket, replaced once a week for 4 weeks (34), led to decreased numbers of spirochetes over an 84-day period. Goodson *et al.* adapted the hollow-fiber technique, using monolythic fibers of various polymers (35). Polyethylene, polypropylene, polycaprolactone, polyurethane, and cellulose acetate propionate monolithic fibers released loaded tetracycline within 24 hr. Ethylene vinyl acetate fibers exhibiting a 9-day release profile have been clinically tested (36). Following removal of fiber delivery systems, bacterial counts in periodontal pockets were extremely low and clinical improvement was significant (37).

The other kind of intrapocket drug delivery system is a slab-type preparation based on polyethylmethacrylic strips (31). Newman *et al.* (38) compared metronidazole acrylic strips and dialysis tubes. Dialysis tubes containing 0.5% metronidazole and acrylic strips loaded with 40% metronidazole both significantly reduced bleeding index and pocket depth for at least 8 weeks after application. With both drug delivery systems, spirochete levels were decreased compared to the controls (39).

Friedman and Golomb developed another slab-like device based on an ethylcellulose matrix (40). The *in vitro* and *in vivo* release kinetics of a wide range of antibacterial agents, including chlorhexidine, metronidazole (28), minocycline (41), and tetracycline (42), were studied in such systems. By adjusting the matrix structure, controlled drug release was attained for periods of between 2 and 205 days. Drug release profiles were modulated by varying initial drug concentrations and film thicknesses, employing different casting solvents, and by adding release enhancers.

Ethylcellulose slabs containing chlorhexidine (29), tetracycline (42), or minocycline (41) were introduced into the periodontal pockets for a period of up to 9 days in three different clinical trials. Various clinical parameters—plaque index, bleeding on probing, and pocket depth—were measured. In addition, bacterial samples were examined by dark-field microscopy and anaerobic cultures were established. Marked reduction in pocket depth and decreased levels of spirochetes and motile rods, with a concomitant fall in the total anaerobic count, were recorded 12 weeks posttreatment.

All the intrapocket devices mentioned above are nondegradable. Degradable intrapocket devices have several advantages compared to nondegradable ones. Patients do not have to return to the periodontist to have these devices removed, making them effective on a time-cost basis as well as generating a high level of compliance. Extraction of nondegradable devices from the pockets can be a complicated and painful procedure. The periodontist must ensure that the nondegradable device is completely removed since remnants can generate a foreign body response at sites that are already inflamed. As noted above, drug evacuation from the nondegradable devices is always incomplete, the total amount released varying. In contrast, with degradable devices, all the loaded drug in the film is eventually released. The latter system is therefore more effective for accurately regulating the dosage reaching the target sites.

Steinberg *et al.* (32) developed a degradable sustained-release intrapocket delivery system. Chlorhexidine release from a cross-linked protein matrix varied as a function of the density of the cross-linking. Drug release from films of low cross-linking density reached 90% of the total within 15 hr, whereas in highly cross-linked films, it extended over 90 hr. Noguchi *et al.* proposed a different kind of degradable film for treating periodontal disease (43). Release rates of both tetracycline and chlorhexidine from a hydroxypropylcellulose matrix were rapid, with evacuation of almost all the drug within 2 hr. However, clinical tests with chlorhexidine in such films indicated that the decreases both in gingival index scores and in the proportion of *Bacteroides asaccharolyticus* persisted for 6 days. Degradable intrapocket drug delivery devices based on other polymers, including hydroxypropyl cellulose, polylactic acid, polycaprolactone, and copolymers of caprolactone with lactide, supplemented with tetracycline, have also been developed (44). The *in vitro* release profile were first order and zero order for monolithic and coaxial fibers, respectively. However, clinical data relating to these systems have not been published to date.

CONCLUSION

Applying drug delivery based on controlled-release technology to the oral cavity has far-reaching clinical implications. In view of the localized nature of dental disease and ease of accessibility to the oral cavity, it should be possible to utilize a greater variety of more sophisticated devices than at other sites in the body. This review describes approaches along these lines directed toward therapy of two primary conditions—dental caries and periodontal disease. However, the potential of such drug delivery systems in other specialties, including oral medicine, endodontics, orthodontics, and oral surgery, remains largely unexplored.

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