REVIEW ARTICLE

Accepted 31 December 2002
Revised 16 September 2002
Received 14 March 2002
Indian J. Pharm. Sci., 2003, 65(2): 106-112

Site Specific Delivery Systems for the Treatment of Periodontitis

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Periodontal diseases are conditions that affect the supporting structures of the teeth. Advances in understanding the etiology and pathogenesis of periodontitis have led to the development of a number of targeted systems for administration of drug into the periodontal pocket. This article reviews the various types of targeted delivery devices (both degradabte and non-degradable), which deliver the therapeutic agents directly to the periodontal pocket. Improvement in clinical and microbiological parameters and reduction in dose have been reported with these systems.

Periodontitis is an inflammatory disease of the supporting structures of the teeth namely periodontal ligament, cementum, alveolar bone and gingival tissues. The disease state is characterized by the destruction of the supporting collagen of the periodontium, resorption of the alveolar bone and formation of periodontal pockets due to migration of gingival epithelium along the tooth surface. Alveolar bone resorption and breakdown of the structural support system is followed eventually by tooth loss[1]. The clinical signs of periodontal disease include swelling of the gingiva, bleeding upon probing and formation of periodontal pocket. This pocket provides an ideal environment for the growth of anaerobic pathogenic bacteria such as *Actinobacillus actinomyceterncomitans, Bacteroides gingivalis, Bacteroides melaninogenicus subspecies intermedius, Porphyromonas gingivalis* and *Prevotella intermedia.*

Periodontal pockets are easily accessible and are therefore a convenient site for localized drug delivery system, which could be inserted into the pocket[2-4]. The basic goal of periodontal therapy is to remove the plaque deposits from the tooth surface and control the pathogenic bacteria to an acceptable level. With systemic antibiotic therapy there is considerable variability in the therapeutic activity due to such factors like poor absorption in the gastrointestmal tract, first pass metabolism, systemic distribution, bacterial sensitivity and resistance. Some studies also report poor results due to the fact that the active product does not reach an adequate concentration at the site of action as it is not retained locally for a sufficient period of time[5]. Infact systemic therapy dilutes antimicrobial agent several thousand folds before it reaches the diseased site, necessitating the ingestion of large doses. The increased toxic effects at these elevated dose levels make systemic administration unacceptable due to low benefit to risk ratio[6]. These drawbacks can be markedly reduced if antimicrobial agent to be used is applied locally, although unwanted effects such as gastrointestinal disturbances and development of antibiotic resistance cannot be totally ruled out. Concentration of drug in tissues can be enhanced incorporating the active agent into controlled release delivery system and placing them directly into the periodontal pocket[7].

A targeted or site specific delivery system aims at delivering the therapeutic agent at sufficient levels inside the pocket and at the same time minimizing the side effects associated with systemic drug administration. Inspite of clinical success, the currently available controlled release formulations suffer from several disadvantages including:

1. Removal of the drug delivery system (formulated from non-biodegradable polymers) at the end of the treatment.

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2. Poor retention of the oil-based delivery systems in the periodontal pocket.

3. The risk of harmful effects on the periodontal tissues due to additives leached out from the polymeric drug delivery system.

Targeted drug delivery systems based on bioadhesive polymers have been widely investigated for use as intrapocket devices in the management of periodontal disease. These show good retention within the aqueous environment of periodontal pocket. A bioadhesive gel formulation based on 4% carbopol containing 1% clindamycin hydrochloride was evaluated *in vivo* on microbial flora of periodontal pockets deeper than 5 mm and significant reduction in microbial count was reported[8]. Bioadhesive semi-solid systems based on hydroxy ethyl cellulose (HEC) and poly vinyl pyrrrolidone were formulated and studied for release rate and it was observed that increased concentrations of HEC decreased the rate of release of tetracycline due to concomitant increase in product viscosity and subsequent decreased rate of penetration of dissolution fluid into the formulation[9]. A bioadhesive delivery system based on copolymer of acrylic acid and poly (ethylene glycol) monomethyl ether monomethacrylate and containing metronidazole for local treatment of periodontitis is under investigation[10]. Bioadhesive disks of cetyl pyridinium chloride were prepared using Bioadhesive polymers like sodium carboxy methyl cellulose DVP and hydroxy propyl methyl cellulose K4M. The purpose of designing the erodible disk was to obviate the need for removal of exhausted device[11]. Brombeig *et al.*[12] formulated a composite wafer that contained poly (lactic-co-glycolic acid) as the main bioerodible component and polymers like starch, sodium carboxy methyl cellulose in combination with silver nitrate served as adhesive coating to the teeth. Such an adhesion resulted in prolonged residence time of the wafer in the periodontal pocket.

Site specific delivery systems:

An intrapocket sustained release device is an ideal approach to achieve controlled delivery of antimicrobials at a desired site. Such a device should meet the following requirements[13]:

1. It should release the therapeutic agent at sufficient levels over the required period of time.

2. The size of the intrapocket device should confirm well with the size and depth of the periodontal pocket.

3. It should be free from undesirable side effects.

4. The drug of choice should be highly specific against the pathogenic microorganisms and should not lead to the development of resistant strains.

5. The device should be such that it is readily acceptable by the patient. It is desirable to have a biodegradable drug delivery system thereby obviating the need to remove any undisintegrated device at the end of treatment.

6. It should not be bulky and should not be exposed beyond the gingival margin.

7. The device sould allow easy insertion into the pocket with minimal pain and discomort.

8. The device should allow the patient to follow the normal oral hygiene procedures such as tooth brushing.

The rate of release from the intrapocket device should be biphasic that is a higher rate of release initially to achieve the desired therapartic level followed by a moderate release profile that maintains the therapeutic levels. Periodontal local delivery devices that have been fabricated for the targeted delivery of antimicrobial agents include fibers, strips and compacts, films and injectable systems (micro particles and gels)[7].

Fibers:

Fibers used for the treatment of periodontitis can be categorized into two types, hollow fibers and monolithic fibers. Hollow fibers comprise of the reservoirs without rate control delivery filled with a therapeutic agent. In these the therapeutic agent is released simply by diffusion through the reservoir wall[14]. Goodson's first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline[15]. Reduction in spirochete numbers and a reduction in clinical signs were produced by these fibers when placed into the periodontal pocket[16]. However the hollow fiber system released the drug very rapidly and was not very successful at sustaining the drug release. Monolithic fibers were essentially developed to retard drug release[16]. Monolithic fibers made of ethylene vinyl acetate loaded with 25% tetracycline hydrochloride were placed to fill the periodontal pocket of 10 patients, which was covered with a periodontal dressing. The average concentration of tetracycline in pocket after 10 d was 643 μg/ml and the total count of pocket microflora was depressed to a level near the limit of darkfield microscopy[17].

Strips and compacts:

Acrylic strips have been fabricated using a mixture of polymer, monomer and different concentrations of antimicrobial agent. The strips were fabricated either by solvent casting or pressure melt method. Strips containing tetracyline, metronidazole or chlorhexidine demonstrated a decrease in the number of motile rods, notably spirochetes[18]. In a later development, the evaluation of amoxycillin-clavulainic acid loaded acrylic strips is reported[19]. Highest level of antibacterial agent was released during the first 24 h period followed by release of therapeutic level of the drugs for a subsequent nine day period. Effect persisted even after 3 w of removal of the acrylic strips[6].

Films:

Films of various polymers have been made tor the controlled release of the therapeutic agents. Sustained release devices composed of crossinked fish gelatin (byco protein) containing chlorhexidine diacetate or chlorhexidine hydrochloride have been developed by Steinberg *et al.*[20] Films based on synthetic biodegradable polymers such as poly (lactide-co-glycolide) (PLGA) containing tetracycline have been developed for modulated release of the drug[21]. A different pharmaceutical approach for the delivery and the release of a drug in the periodontal pocket is a slab-like device[13]. The advantages of such a device include ease of insertion, dimensions that confirm well with the dimensions of the pocket and minimum pain on insertion.

Injectable systems:

These systems allow easy application of the therapeutic agent using a syringe. They are also cost-saving. These can be grouped into following two categories:

Microparticles:

Microparticles based systems of biodegradable poly alpha hydroxy acids such as poly lactide (PLA)or poly (lactide-co-glycofide) (PLGA) containing tetracycline have been designed for periodontal disease therapy[22]. PLGA microspheres containing minocycline have been formulated and have been used for the elimination of *Porphyromonas gingivalis* from periodontal pockets.

Gels:

Mucoadhesive, metronidazole containing gel systems designed for periodontal treatment and based on hydroxyethylcellulose, Carbopol 974 and Polycarbophil have been described[23]. The gel is applied subgingivally with the help of blunt cannula and syringe. The gel is only marginally effective in decreasing the anaerobic bacterial count. This may be due to low number of bacteria susceptible to metronidazole or due to the presence of bacterial biofilms. An injectable lipid-like vehicle based on glycerol mono-oleate and sesame oil containing 25% metronidazole (Elyzol) has become available with supportive evidence of efficacy. This product can be injected into the periodontal pocket where the thixotropic agent changes to gel[24]. Gel formulations of minocycline 2% are available under various trade names such as Periocline (Sunstar Company Limited, Osaka, Japan) and Dentomycin (Lederle Lab, U.K). Table 1 gives a list of different systems used as intrapocket devices.

***In vitro* evaluation of devices:**

The *in vitro* characterization of an intrapocket device includes study of parameters such as general appearance and texture, dimensional variation, weight variation, content uniformity, surface pH, measurement of bioadhesion and *in vitro* dissolution profile[47]. Folding endurance and Percentage elongation at break are evaluation parameters specific for film. Accurate evaluation and analysis of sustained release profile of an intra-pocket device requires proper designing of an *in vitro* drug evaluation system[7].

The *in vitro* characterization of a newly developed bioadhesive patch for controlled delivery via the buccal mucosa was investigated by Guo *et al.*[48] They developed buccul patches of Carbopol 934P and studied the effect of difierent ratios of bioadhesive supporting polymers on the surface properties, adhesion and swelling of buccal patches. Various *in vitro* methods of evaluation are summarised in Table 2.

***In vivo* evaluation of devices:**

The bioerodible polymer insert fix the controlled release of metronidazole was evaluated *in vivo* using a rat model. Polymer implants containing 10% metronidazole were prepared from cellulose acetate phthalate/Pluronic L101 with 50/50 and 30/70 polymer blends ratios. In all *in vivo* experiments, no signs of adverse tissue reactions were detected. Based on these results prototype delivery inserts were designed and subsequently evaluated in volunteer patents. Preliminary results from this pilot study stated that the metronidazole concentration in Gingival Crevicular Fluid (GCF) was significant throughout the sampling period of 3 h and remained well above the Minimum Inhibitory Concentration (MIC) for most periodontal pathogens[49].

A preliminary clinical study designed to test the performance of tetracycline-poly (lactide-co-glycolide) films *in vivo*

was performed using eight periodontal maintenance patients aged 35 to 65 y[52]. All patients had at least one probable, periodontal pocket measuring at least 5 mm in depth in each jaw quadrant that bled on gentle probing. None of the subjects had received periodontal maintenance therapy within the last six months. The periodontal pockets chosen as experimental sites were isolated with cotton rolls, rinsed and wiped of plaque and debris, and dried with cotton pellets and an air syringe. GCF was measured with a crevicular fluid strip and measuring instrument (Harco Electronics, Tustin, CA). Each subject received a film containing either 0% or 25% w/w tetracycline hydrochloride, which was inserted into one periodontal pocket located in each jaw quadrant. From the results of the *in vivo* evaluation, it was found that therapeutic drug concentration in excess of the MIC (8 μg/ml) was maintained in the GCF for a period of at least 14 d.

No evaluation of an intrapocket device is complete without a correlation between the release rate constant or some

TABLE 1: CONTROLLED DELIVERY SYSTEMS AS INTRAPOCKET DEVICES IN PERIODONTAL DISEASE.

Drug(s)/Type of device	Fabrication Technique/Polymer	Product Name	References
Tetracycline microtubules	Microencapsulation, diacetylenic phosphatidyl cholines	-	25
Tetracycline monolithic fiber	Melt extrusion, ethyl vinyl acetate copolymer	Actisite (Alza Corporation)	26-28, 17
Doxycycline gauze	Equilibration in drug solution, bioabsorbable dental materials	-	29
Tetracycline, Chlorhexidine film	Cast from ethanol solutions, hydroxy propyl cellulose	-	30
Tetracycline films, sponge gel	Cast from aqueous solution cross-linked with gluteraldehyde, Atelocollagen	-	31,32
Chlorhexidine, Tetracycline films	Cast from water-ethanol mixture crosslinked with gluteraldehyde, Byco protein	-	21
Ofloxacin strip	Methacrylic acid particles dispersed in a HPC film, hydroxy propyl cellulose (HPC) methacrylic acid copolymeres	PT-01	33,34
Tetracycline, Metronidazole compacts	Direct compression, polyhydroxy-butyric, polydroxyvalerate, polylactic acid, polymers and copolymers	-	35
Chlorhexidine gluconate inserts	Cross-linked hydrolyzed gelatin and glycerin	Periochip (Perio Products Ltd)	36
Tetracycline microcapsules	Solvent evaporation, lactic acid/glycolic acid copolymers	-	37
Metronidazole lipid-like gel	Mixing, glycerylmono-oleate/ sesame oil	Elyzol (Dumex- At Alpharma)	24,3 8
Clindamycin film	Cast from ethanol: water mixture, Eudragit L and Eudragit S	-	39
Minocycline lipid-like gel	Mixing, Hydroxy ethyl cellulose, aminoalkyl methacrylate copolymer triacetine, magnesium chloride, glycerin	Dentomycin (Lederle Lab), Periocline (Sunstar Co. Ltd)	40-43
Doxycycline hyclate, sanguinarium liquid system	Poly (DL-lactide) dissolved in N-methyl-2-pyrrolidine (NMP),polylactic acid	Atrigel, Atridox (Atrix Lab)	44-46

TABLE 2: SUMMARY OF VARIOUS *IN VITRO* METHODS FOR EVALUATION.

Drug/Sustained release delivery system	Polymer	*In vitro* method	References
Metronidazole bioerodible polymer insert	Blends of Cellulose acetate phthalate and Pluronic L101	Rotating-disk apparatus (modified Hannson dissolution apparatus with the paddles replaced by rotating sample holders) was used.	49
Salicylic acid, caffeine, tripelennamine film	Polyethylene glycol-ethyl cellulose	Membranes were attached to glass plates with a silicon pressure sensitive adhesive and release rate determined in 500 ml of buffer solution per heated to 37°.	50
Chlorhexidine diacetate film	Ethyl cellulose	Two films were clamped between the compartments of dissembling dissolution cells containing solution warmed to 37°.	51
Minocycline films	Ethyl cellulose	Films were shaken in orbital shaker using water as the elution medium.	52
Ofloxacin controlled release insert (PT-0l)	Methacrylic acid copolymers (MACS), hydroxy propyl cellulose	Rotating basket method of the Pharmacopoeia of Japan was used. 500 ml of deaerated 12.5 mM phosphate bufler (pH 7.2) was used as the dissolution medium at 37°.	33,34
Amoxycillin-clavulanic acid strips	Acrylate	Strips were incubated at 37° in 3 ml distilled water contained in Bijoux bottles.	19
Tetracycline films	Poly (lactide-co-glycolide)	Differential dissolution studies were carried out in Kolthofs borax -phosphate buffer pH 7.3, contained in screw capped, 10 ml test tubes agitated at 1 rpm in a water bath at 37°.	53
Amoxycllin trihydrate fibers	Poly vinyl acetate	Fiber was incubated at 37° in 50 ml of isotonic phosphate buffer (pH 6.6) and agitated at 50 rpm in a shaking water bath.	54
Silver nitrate, benzyl penicillin, tetracycline composite wafers	Poly (lactide-co-glycolide), ethyl cellulose	Wafer was incubated at 37° in a vial with 1 ml of deionized water/human serum and then continuously shaken at 250 rpm using a KS-10 orbital shaker (BEA-Enrotech Hyde Park, MA, USA).	12
Chlorhexide gluconate gel/ film	Chitosan	Bioadhesion was determined using freeze dried films and gels on fresh porcine buccal mucosa. The maximum force of detachment was measured on a texture analyzer (TA-XT2, Stable Microsystem)	55

Cetyl pyridinium chloride disks	Sodium carboxy methyl cellulose DVP, hydroxy propyl cellulose K4M	The duration of bioadhesion was determined on a self designed flow through cell consisting of a cavity at the lower base for placement of bovine mucosal membrane and disk. Isotonic phosphate buffer of pH 6.6 simulating the salivary pH was pumped at a flow rate of 0.65 ml/min. Duration of bioadhesion was determined by measuring the time required for the formulation to erode completely.	11

parameter of it and a well-defined quantitative *in vivo* data[6]. This requires an estimation of drug concentration in the periodontal pocket fluid and changes in clinical and microbiologic parameters. An earlier report suggests that *in vivo* drug release can also be estimated by removing fractions of the device periodically after placing it in the periodontal pocket and replacing it again. But the high discrepancy between the *in vivo* and *in vitro* release is attributed to the high degree of error in cutting fractions from the original sustained release device[49].

CONCLUSIONS

The controlled delivery devices are a useful adjunct to the conventional surgical or non-surgical treatments but are no substitute for these measures[7]. Despite the number of delivery systems investigated for use in periodontal disease, an ideal targeted delivery system is yet to be developed. The greatest advantage associated with the use of intrapocket delivery systems has been that administration is less time consuming than mechanical debridement, and treatment does not rely, as heavily on patient compliance as is the case with conventional topical delivery systems such as sub-gingival irrigation. Also, the amount of drug required to achieve effective concentration in the GCF is considerably less than that required if the drug is delivered systemically[4].

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