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Review Article

Current Status of Local Drug Delivery Systems in the Treatment of Periodontal Diseases

Dk Siti Najwa Rashidah Pg Hj Ismail[1], Rajan Rajabalaya[1], Sheba R David[1] and Jagjit Singh Dhaliwal[1]*

*[1]PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link BE1410, Brunei Darussalam

***Correspondence Author:** Dr. Jagjit Singh Dhaliwal, PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link BE1410, Brunei Darussalam; **Email:** jagjit.dhaliwal@ubd.edu.bn

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Abstract

Periodontal disease includes many pathological conditions affecting the periodontium, but gingivitis and periodontitis are the more common types. Gingivitis is a progressive condition, although it is reversible, when left untreated it can lead to periodontitis. Microbial species have a major role in the aetiology of periodontitis.

Method: Information was derived from research papers using PubMed, Science Direct, and Google Scholar using the keywords local drug delivery system, treatment, and periodontal disease. The search included articles up to 2018 with majorly in vivo studies in patients with periodontitis. The usage of local drug delivery systems with controlled or sustained release mechanisms may provide slightly better therapeutic effect in comparison with patients who undergo scaling and root planning only.

Conclusion: The present review of the literature of the currently available local drug delivery systems in the treatment of periodontal diseases.

Keywords: *Gingivitis, Periodontal Diseases, Periodontium, Scaling*

Introduction

Periodontal disease is a term which comprises several pathological conditions involving the periodontium, which includes the gum, alveolar bone, dental cementum, and periodontal ligament [1]. The more common conditions of periodontal diseases are gingivitis and periodontitis. Periodontal disease is the most prevalent oral condition of the worldwide population, with gingivitis affecting 50% to 90% of adults [2,3]. Gingivitis is the mildest type of periodontal disease. It is a localised inflammation of the gum tissue (gingiva) caused by bacteria in the dental plaque, which is a microbial biofilm that forms on the teeth and the gingiva. Cultural studies have shown that there are more than 700 distinct microbial species that can be found in the dental plaque, although only a small group has been confirmed to contribute to the cause and progression of periodontal disease [3,4]

Gingivitis, when left untreated, can progress to periodontitis [3,5]. Unlike gingivitis, which is confined to the gingiva, periodontitis leads to the loss of connective tissues supporting or surrounding the teeth. This loss of gingiva, alveolar bone, and periodontal ligament creates deep "pockets". When these deep periodontal pockets have formed and is filled with microbes, the condition becomes highly irreversible, and eventually may lead to loss of teeth [5].

Literature Research

Search strategy

A literature search with several restrictions was done electronically through the following databases: PubMed, Google Scholar, and Science Direct, using search terms that have been summarised in (Table 1).

Table 1. Number of results yielded by searching using keywords through three different databases.

Database	Search term(s)	Number of results
PubMed	(local drug delivery system) AND periodontal disease	149
	(local drug delivery system) AND "periodontal disease"	38
	(local drug delivery system [Title/Abstract]) AND periodontal disease [Title/Abstract]	6
Science Direct	local drug delivery system in treatment of periodontal disease	2,458
	"local drug delivery system" AND "periodontal disease"	46
	"local drug delivery system" AND "treatment of periodontal disease"	20
Google Scholar	local drug delivery system in treatment of periodontal disease	58,600
	"local drug delivery system" AND "periodontal disease"	807
	"local drug delivery system" AND "treatment of periodontal disease"	321

Inclusion and exclusion criteria

The search was restricted to research articles written in English, and the search included studies from 1979 up to 2018, since 1979 was

the year that local drug delivery systems were first considered. Apart from articles that do not meet the criteria mentioned, animal studies were also not included.

History of Treatment

As mentioned previously, it has been proven that the bacteria-filled film is one of the main causes of periodontal diseases. The traditional methods of non-surgical treatment of periodontal disease, including mechanical scaling and root planing, did not guarantee improvements of the disease. Treatment of periodontitis focuses mainly on reducing the total microbial count, hence scaling and root planing needs to have an adjunct therapy, in other words, the antimicrobial agents. It was Dr. Max Goodson who pioneered and developed the concept of local drug delivery systems in 1979 [6]. This discovery has led to the increase of studies regarding local drug delivery systems pertaining to periodontal disease in the last decade.

Advantages of local antimicrobial drug delivery directly into periodontal pocket

The advantages of delivering antimicrobial agents directly to the target instead of taking systemic agents [7,8]. These are included and not limited to direct access to the targeted diseases, first-pass metabolism is bypassed, avoids problems regarding the gastrointestinal system, which is a common occurrence with drugs that are orally administered, able to provide more rapid absorption because of the rich blood supply' reduction in cost of treatment, less chances of antimicrobial resistance and suitable for patients who cannot swallow. However, there are still some limitations, which include inability to administer local irritants, limited dose because of the small area and cost to manufacture delivery devices may get expensive.

Local drug delivery systems

Drugs that need to be delivered locally are done so by inserting them into a vehicle in the form of fibres, gels, strips, among others, which will be discussed in Table 2 below. The ideal characteristics for that are desired for a local anti-microbial agent are able to deliver the drug to the target, in other words, the base of the pocket, has a therapeutic concentration in the pocket, able to maintain the concentration of drug for a period of time where the drug gives therapeutic effect and exhibits little side effects.

Fibres

Fibres are thread-like devices with a reservoir-based sustained release system. They are circumferentially placed inside the periodontal pockets using an applicator, and to ensure the controlled release of drug, the fibres are secured by applying cyanoacrylate as an adhesive [9].

Actisite®

Actisite was introduced in 1994 and was the first controlled-release antimicrobial product to be commercialised. It is 23 cm long and 0.55 mm wide, delivering 12.7 mg of tetracycline hydrochloride. The fibre is non-biodegradable and has to be removed after 10 days, which is the end of the therapy. In comparison with 250 mg of tetracycline delivered orally which results in 1 μg/ml in the gingival crevicular fluid, the locally delivered Actisite achieves an initial concentration of 1590 μg/ml in the periodontal pocket. The concentration level remained at a mean of 1300 μg/ml for 7 days [7]

Films

Film is a form of matrix delivery system where the drug is distributed throughout the polymer, and it is released by either drug diffusion, or erosion or dissolution of matrix. This system is more commonly used as it has several advantageous characteristics. The size and shape of the films is flexible it can be easily changed to fit the dimensions of pocket needed to be treated. Larger-sized films can be applied onto the cheek mucosa, or they can also be divided into smaller sizes to be placed into the pocket [9].

Injectable systems

Injectable systems have an added advantage of easy and rapid application. Antimicrobial agents can be delivered using a syringe directly into the periodontal pocket, without the patient experiencing pain. The cost and time taken for the therapy is also considerably lower when compared to delivery systems that need to be applied securely. Furthermore, the injectable system should be able to fill the pocket, hence reaching more pathogens [48].

Gels

Gels are semisolid mucoadhesive systems that have also received attention for the targeted delivery of antimicrobial agents, offering some advantages [8]creation of periodontal pocket and resorption of alveolar bone, resulting in the disruption of the support structure of teeth. According to WHO, 10–15% of the global population suffers from severe periodontitis. The disease results from the growth of a diverse microflora (especially anaerobes. For instance, in terms of preparation and administration, they are easier to prepare. A downside is that gels have faster drug releasing rates. Gels are applied sublingually using a blunt cannula and a syringe [48].

Strips and compacts

Strips are thin and elongated matrix bands where the drug will be distributed throughout the system. Acrylic strips filled with different antimicrobial agents have been developed, and those containing tetracycline or metronidazole were found to have best improved the parameters of periodontitis [49].

Vesicular liposomal systems

Vesicular liposomal systems are investigated intently in order to be used in periodontal diseases. This is because they are designed to mimic the bio-membranes in terms of structure and their behaviour [9].

Microparticle systems

Microspheres are solid structures that are spherical in shape, with sizes ranging from 1 to 1000 μm. The drug is dispersed throughout the matrix. To prepare microspheres, non-biodegradable and biodegradable materials are both being investigated. These materials

Table 2. Summary of some local drug delivery systems [9].

Local drug delivery system	Polymer matrix	Incorporated drug	Reference
Fibres	Cellulose acetate	1. Tetracycline HCl 2. Chlorhexidine	[6] [10]
	Ethylene vinyl acetate	Tetracycline HCl	[11]
	Poly-(Ɛ-caprolactone) (PCL)	Tetracycline HCl	[11]
Films	Ethyl cellulose	1. Metronidazole 2. Tetracycline HCl 3. Minocycline	[12] [13] [14]
	Cross-linked atelocollagen	Tetracycline	[15]
	Gelatin (Byco® protein)	Chlorhexidine diacetate	[16]
	Collagen	Chlorhexidine gluconate	[17]
	Chitosan	Taurine	[18]
	Chitosan + Polylactide-co-glycolic acid (PLGA)	Iproflavone	[19]
	Chitosan + PCL	Metronidazole	[20]
	Polyvinyl alcohol + carboxymethyl chitosan	Ornidazole	[21]
	PLGA	1. Tetracycline 2. Amoxycillin + metronidazole	[22] [23]
	Eudragit L® and Eudragit S®	Clindamycin	[24]
	PCL	Minocycline	[25]
Gels	Chitosan	Metronidazole	[26]
	Hydroxyethyl cellulose + polyvinylpyrrolidone	Tetracycline	[27]
	Poloxamer 407 + Carbopol 934P	Propolis	[28]
	Poly(α-lactide) + *N*-methyl 2-pyrrolidone	1. Sanguinarium 2. Doxycycline hyclate	[29] [30]
	Glycerol monooleate + sesame oil	Metronidazole	[31]
	PLGA	Tetracycline	[32]
Strips	Polyethylmetha acrylate (acrylic)	1. Tetracycline HCl 2. Metronidazole	[33] [34]
	Hydroxypropyl cellulose	1. Chlorhexidine, tetracycline 2. Doxycycline	[35] [36]
	Hydroxypropyl cellulose + methacrylic acid	Ofloxacin	[37, 38]
	Polyhydroxybutyric acid	Tetracycline HCl	[39]
	PLGA	Tetracycline HCl	[40]
	Xanthan	Chlorhexidine	[41]
	Ethyl cellulose	Chlorhexidine	[42]
Vesicular liposomal systems	Phosphatidylinositol	Triclosan	[43]
	Immunoliposomes	Anti-oralis	[44]
Microparticle systems	PLGA	Tetracycline	[45]
Nanoparticle systems	PLGA	Triclosan	[46]
	Cellulose acetate phthalate	Triclosan	[46]
	Chitosan	Antisense oligonucleotide	[47]

include natural polymers, modified natural substances, and synthetics. They can be formulated into chips, dental paste, or even directly injected into the targeted area [8,49]creation of periodontal pocket and resorption of alveolar bone, resulting in the disruption of the support structure of teeth. According to WHO, 10–15% of the global population suffers from severe periodontitis. The disease results from the growth of a diverse microflora (especially anaerobes.

Nanoparticle systems

Nanoparticles have sizes ranging from 10 to 1000 nm, which enables them to penetrate through regions that may not be reached by other delivery systems. This is a major advantage above the other systems like microparticles, since the ability to reach these otherwise neglected areas result in a decreased frequency of administration and it also provides a more uniform distribution of the drug [9]. For most of the local drug delivery systems, there is only a limited number of studies that have been published. Even though there are studies available, it is difficult to compare between different trials as the therapy given to the participating patients vary greatly.

Conclusion

Local delivery drug systems are seemingly a good alternative to deliver antimicrobial agents compared to systemic delivery. They produce fewer side effects, which could improve patient compliance. Since there are no studies proving the effective use of locally delivered drugs as a monotherapy, local drug delivery system remains to be a good adjunct therapy.

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