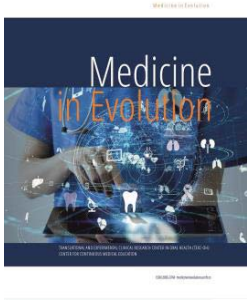
Sustained-release delivery of antimicrobial drugs for the treatment of periodontal diseases: a narrative review



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Abstract

The inflammatory condition known as periodontitis can seriously impair a patient's quality of life and the oral cavity if left untreated. Although there isn't a reliable, standardized treatment for periodontitis, there have been numerous attempts, including tissue regeneration methods, antibiotics, and subgingival instrumentation. Given the limitations of the aforementioned treatment, local drug delivery systems appear to be the way of the future. These systems have the potential to release both tissue regeneration inducers and antibiotics gradually over time.

Keywords: local drug delivery agents, periodontitis, antibacterial agents, biofilms

INTRODUCTION

Pharmaceutical formulations that control the release rate of therapeutic substances over a predetermined length of time are known as sustained-release drug delivery systems. The terms sustained release, slow release, extended release, prolonged release, controlled release, time release, and delayed release are used interchangeably in the literature and in business to refer to these dose types [1]. The rate at which a medication is released from its pharmacological carrier determines its pharmacokinetics at a target site. The majority of pharmaceutical drug delivery systems are created to deliver the drug, not to regulate its release within the intended organ. Drug carriers in and of themselves include, for instance, tablets, capsules, gels, lotions, ointments, injections, and inhalers [2]. Furthermore, the majority of toothpastes, mouthwashes, and tablets used in the dentistry industry are merely drug carriers; they have no control over how quickly the active ingredients are released [1].

Aim and objectives

This review aims to pinpoint the existing obstacles and potential areas for further investigation, specifically with the use of local drug delivery system (LDDSs) with different characteristics in the treatment of periodontitis, with or without accompanying systemic disorders.

MATERIAL AND METHODS

To include articles in this review, we used the following search engines: PubMed and Google Scholar. We used the following keywords: local drug delivery, LDDS, slow-release, and periodontitis. The total number of articles found was 963 on PubMed and 1901 on Google Scholar, published from 1979 to 2024. Out of the total number of articles, specifically, 129 articles were chosen for the current review. This selection was made after removing duplicate papers and the ones that did not meet the criteria for item selection. Titles and abstracts were assessed by no less than two independent researchers for the purpose of inclusion. All items that successfully passed the initial screening were requested in their entirety. Two researchers assessed each complete article to determine if it should be included or excluded.

RESULTS AND DISCUSSIONS

1 Local drug delivery systems

Systemic medication delivery has proven effective in treating periodontitis during the past 50 years [3,4]. However, the utilization of systemic administration for medications presents several drawbacks, including dysbiosis and insufficient drug concentrations at the desired region. Nevertheless, this can lead to gastrointestinal issues, medication resistance, and toxicity [5-7]. Over the past three decades, there has been a growing interest in studying local drug delivery systems (LDDSs) to explore the targeted usage of pharmaceuticals at specific sites and the regulation of their release. Polymers were found as medication carriers for this specific purpose. They possess the ability to protect the bioactive agents while being delivered into the body and also have the capability to control the rate at which they are released. The bioactive compound can either be encapsulated within the polymeric matrix or chemically bonded to the polymeric chain [8]. Drug delivery systems provide precise regulation and extension of drug release at an applied location and can also be encapsulated within multiple target agents concurrently. By doing so, it is feasible to decrease both the dosage and frequency of drug administration [9,10]. An LDDS offers more advantages

compared to systemic delivery. LDDS has the ability to circumvent gastrointestinal issues and the body's metabolic processes, allowing medications to directly reach the desired location. This results in increased effectiveness of the treatment [11,12]. Furthermore, LDDS enables the noninvasive administration of drugs in the subgingival pockets [13]. In addition, this method of drug administration enables the simultaneous delivery of two or more pharmaceuticals from distinct categories into the periodontal pockets. Twenty-three LDDS can have several forms, including fibers, irrigations, membranes, films, nanoparticles (NPs), and microparticles. The LDDS, which provides therapeutic benefits for periodontal problems, consists of three primary classes of medications: antibacterial, inflammation-modulating, and alveolar and bone regenerating agents [13].

2 Types of LDDSs in Periodontitis Treatment

1. Fibers

Fibers serve as a reservoir-type delivery system that contains a specific therapeutic substance. They are inserted into the periodontal pocket using an applicator and held in place by either a cyanoacrylate glue or a periodontal dressing [14]. Several polymers have been suggested and examined as fibers for localized drug delivery systems. These include both natural polymers, such as chitosan, zein, and gelatin, as well as synthetic polymers including poly(e-caprolactone), polyurethane, polypropylene, cellulose acetate propionate, and ethyl vinyl acetate [14,15]. Each of them, upon utilization and examination, was infused with antibacterial medications.

2. Matrix system: Strips and Films

Strips and films are small sections made of a matrix material in which pharmaceuticals are uniformly dissolved. Strips and films are highly effective in conforming to the shape and dimensions of the periodontal pocket, making them easy to insert with minimal patient discomfort. They are specifically put within the interproximal periodontal pocket region [16].

The most used producto is Periochip (Perio Products Ltd., Jerusalem, Israel) is a brownish orange coloured rectangular chip containing chlorhexidine gluconate (2.5 mg) embedded in a matrix of biodegradable polymer – gelatin. It is available in dimensions of 5 × 4 × 0.3 mm weighing about 7.4 mg (drug and polymer). Post-delivery, chlorhexidine (40%) is released (by diffusion) in the first 24 h showing an initial burst effect, following which constant drug release was noted for 7 days.

3. Gels

Gels are semi-solid systems with a low concentration of cross-linked particles, where the active drug molecules are evenly distributed in a solid medium that does not flow under steady conditions [17,18]. Gels are highly regarded in the field of general dentistry for their widespread usage as a carrier system to provide therapeutic drugs for many oral conditions, including oral ulcers, denture stomatitis, and desquamative gingival lesions. The wide range of applications is facilitated by qualities such as the ease of preparation and administration, sustained drug release pattern, minimal dose frequency, and low drug toxicity [19,20]. In the field of periodontics, therapeutic gels containing active agents are carefully administered into the subgingival pocket using syringes with wide port needles. This method ensures that the gel is evenly distributed throughout the affected area.

4. Irrigating systems

The effectiveness of locally administered antimicrobial medications in an irrigation system is contingent upon factors such as the extent of penetration, the severity of the infection, the flow of gingival crevicular fluid (GCF), the concentration of the drug, and the duration of time that an adequate amount of drug is accessible in the pocket region. The proficiency of irrigation devices is determined by the diffusion of the drug into deeper levels of the pocket and the duration of exposure to the antibacterial agent [21]. In supragingival irrigation devices, the irrigating agent reaches a depth of 29-71% in shallow pockets and 44-

68% in moderately deep and deep pockets. On the other hand, subgingival irrigation has a higher penetrability, ranging from 75-93% into deep pockets [21].

5. Microparticulate system

Microparticles are solid spherical structures made of polymers, with a diameter range of 1–1000 µm. They are designed to hold active therapeutic agents, which are evenly distributed throughout the polymer matrix. This design allows the drugs to be protected from the external environment, prevents incompatibility issues, masks unpleasant taste, and improves bioavailability and sustained therapeutic activity [22]. The polymers used for microencapsulation include of biodegradable synthetic polymers such as polyesters and polyanhydrides, as well as natural polymers including chitosan, hyaluronic acid, and alginic acid. Microencapsulation utilizes both water-soluble polymers such as gelatin and starch, as well as insoluble polymers such ethyl cellulose and polyethylene. Polymethacrylates, cellulose esters, and polyvinyl derivatives are examples of enteric coating polymers that are utilized for microencapsulation [22-25]. Microparticles can be administered using several carrier systems such as chips, dental pastes/gel systems, and direct injection into the pocket [25]. Several techniques for formulating microparticles include the solvent evaporation method (single and double emulsion), coacervation and phase separation, and the spray drying method [25–27]. Multiple clinical studies have proven the efficacy of drug-loaded microparticles for treating periodontitis. The utilization of solid lipid microparticles containing lycopene, in conjunction with SRP, has demonstrated favorable clinical outcomes [28]. The study utilized a double emulsion process to generate biodegradable microspheres loaded with Doxycycline. The microspheres had a mean particle size ranging from 90 to 200 µm. The combination of PLGA and PCL in varying percentages was used. The results indicated that both the medication and polymers were stable during the in-vitro release, which lasted for a duration of up to 11 days. The formulation shown substantial enhancement in both the clinical and microbiological aspects for a duration of up to 3 months, in comparison to the commercially available doxycycline gel [29]. A further investigation was conducted on micro-particles containing metronidazole benzoate, which had diameters of 31.0 and 74.5 µm. These micro-particles were then added to chitosan/PCL films. The study found that these films had a release rate of 64% over a period of 7 hours, and also shown strong mucoadhesive properties. This research was documented in reference [30]. A study was conducted on doxycycline hyclate loaded microspheres prepared using the solvent diffusion method of spherical crystallization technique. The study found that there was an initial burst release of 24% on the first day, followed by a sustained release of 52.25% over a period of 7 days. Additionally, the study showed that the microspheres led to a significant reduction in probing pocket depth and P.g. cell count compared to SRP [31].

6. Nanoparticulate drug delivery (NP) system

In the field of periodontics, researchers have conducted investigations on metallic and polymeric nanoparticles, nanofibers, liposomes, quantum dots, and nanocomposites/nanogels. These studies have been carried out both in laboratory settings (in-vitro) and in clinical trials [32]. Metallic nanoparticles (NPs) are produced by reducing metallic salts using chemical reducing agents or by employing green chemistry methods that involve the use of plant resources abundant in antioxidants. Additional biological methods involve investigating the capacity of algae, fungus, bacteria, and viruses to decrease metallic salts into nanoparticles (NP) [33,34]. The nanofiber-based scaffolds are created using several techniques such as electrospinning, emulsion method, mixing, coaxial process, and surface modification. These techniques are used to include therapeutic compounds into the scaffolds, with the goal of achieving certain clinical results in dentistry [35]. The drug release from the nanofibers is determined by the diameters of the fibers, drug diffusion rate, polymer degradation/erosion rates, drug dissolving rates, and drug physical desorption rates. Smart

electrospun nanofibers contain components that undergo physicochemical changes in response to various conditions such as pH value, temperature, light, electrical and magnetic fields. These changes can alter the pace at which drugs are released [36].

CONCLUSIONS

Within its limitation, this research suggests that both in vitro and vivo studies show promising results regarding the use of LDDS in the treatment of periodontal disease. This application leads to an improvement in periodontal clinical parameters. This is attributed to the evolution and improvement of this administration approach over time, as well as the reduced occurrence of adverse effects compared to the systemic administration of other medications. Nevertheless, additional research is necessary to thoroughly evaluate the efficacy of these delivery methods in human subjects and to explore any potential adverse effects in patients, particularly those with systemic illnesses. Thus, future research should focus on how local drug delivery systems can be personalized in order to optimize future clinical protocols in periodontal therapy.

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