

POLYMER-BASED COMPOSITE AS A LOCAL DRUG DELIVERY SYSTEM FOR PERIODONTITIS THERAPY: A BRIEF REVIEW

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Abstract

Periodontitis is a common chronic oral disease which if left untreated may cause mobility to loss of teeth. Periodontitis is local infection so a therapy using a local drug delivery system was more convenient than a conventional drug delivery system because the probability of side effects emergent is bigger. There are some drug delivery system types in periodontitis therapy and basically, these systems are using a polymer as a matrix by inserting a therapeutic agent into it so creating a composite structure. This study aims to provide a brief review of polymer-based composites utilized as local drug delivery systems for periodontitis therapy. A comprehensive literature review was conducted to gather information on the various types of polymer-based composites employed in periodontitis therapy. Key aspects such as polymer selection, drug loading methods, and therapeutic efficacy were analyzed. The results show Polymer-based composites have shown significant potential as effective local drug delivery systems for periodontitis treatment. The choice of polymer matrix, drug incorporation techniques, and release kinetics play crucial roles in determining the therapeutic outcomes. Various polymers, including biodegradable and non-biodegradable ones, have been explored for their suitability in this application, with promising results reported in preclinical and clinical studies.

Keywords: Periodontitis, polymer, composite, local drug delivery system

Introduction

Periodontitis is an inflammation condition on periodontal tissue caused by a specific microorganism, as a result of progressive failure of the periodontal ligament and alveolar bones with a pocket formation, recession, or both (Kwon et al., 2021)(Zięba et al., 2020)(Onisor et al., 2021). Periodontitis is started with an inflammation reaction on the gums (gingivitis) and if it was left untreated, it will evolve involving the periodontal ligament, cementum, and alveolar bones (Ray, 2023).

A therapy for periodontal disease basically tends to omit the pains, inflammations, and bleeding in the gingiva, decreasing the depth of the periodontal pocket along with its infections, slowing down the rate of damage whether on soft tissues or bones, reducing the teeth instability, optimizing the chewing system, and attempted to restore the condition of the damaged tissue in some cases (Dwarakanath, 2019). Periodontitis therapy is basically in the form of 1. A removal of debris mechanically with scaling and root planing; 2. a pathogen organism destruction of intervention metabolism by using antibiotics and antiseptics; 3. changing the environment so that it will be dislikeable by the involved microorganism (Sholapurkar et al., 2020). Scaling and root planning itself will not be enough to eliminate the bacteria from the periodontal pocket, it needs

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antibiotics and antiseptics (locally or systemically). Since periodontitis is a local disease, so local antibiotics and antiseptics therapies are preferable (Sholapurkar et al., 2020).

There are some local drug delivery system types for periodontitis therapy such as irrigation system, fiber, strip and film, microsphere, nanosystem, and gel with all advantages and disadvantages. This conducting system has a polymer component as a matrix and medical content which conducts to create a composite structure (Wei et al., 2021). Based on the description above, the author is interested to do a short review against the polymer-based composite that is used as a therapy for periodontitis. The study aims to provide a brief review of polymer-based composites utilized as local drug delivery systems for periodontitis therapy.

Research Methods

The study used qualitative method with literature study. To conduct a literature review on the use of polymer-based composites as a therapy for periodontitis, the following methods can be employed:

- 1) Identification of Relevant Literature: Search for peer-reviewed articles, review papers, and clinical studies related to the use of polymer-based composites in the treatment of periodontitis. Utilize academic databases such as PubMed, Scopus, and Web of Science to identify relevant literature.
- 2) Inclusion and Exclusion Criteria: Define specific inclusion and exclusion criteria to select the most relevant articles. Inclusion criteria may include articles published in the last 5-10 years, studies conducted on human subjects, and articles available in English. Exclusion criteria may involve studies on animals, articles not related to polymer-based composites, and non-English articles.
- 3) Data Extraction: Extract relevant information from the selected articles, including the types of polymer-based composites used, their effectiveness in periodontitis therapy, potential advantages and limitations, and any clinical evidence supporting their use.
- 4) Data Synthesis: Analyze and synthesize the extracted data to provide a comprehensive overview of the current state of knowledge regarding the application of polymer-based composites in periodontitis therapy. This should include a discussion of the various types of polymer-based delivery systems, their mechanisms of action, and their potential for improving treatment outcomes.
- 5) Critical Evaluation: Critically evaluate the strengths and limitations of the existing literature, including any challenges or unresolved issues related to the use of polymer-based composites in periodontitis therapy.

By following these methods, a thorough literature review can be conducted to provide valuable insights into the use of polymer-based composites as a therapy for periodontitis.

Results and Discussion

Polymer in Drug Delivery System

The local drug delivery system develops since enteric coating sustained release tablets (SR tablets) is introduced in 1935 by Miller and the first commercial controlled drug delivery system is presented by Alza, a medicine for glaucoma therapy (Ocusert) which is Pilocarpine diffused through a polymer membrane (B. Wang et al., 2016). Polymer has been widely used as a drug delivery system because they can have an antibacterial properties like Chitosan which exhibit antibacterial properties against

pathogenic bacteria that can cause periodontitis (Costa et al., 2012). In addition, polymers have many uses, good stability, non-toxic, biocompatible, non-immunogenic, easy and relatively cheap to fabricate and manipulate, and are easy to shape according to the shape of a deep periodontal pocket (Chi et al., 2019). Polymer is used to develop various drug delivery systems in particle formation (micro and nano), micelles, hydrogel, tablets, capsules, etc (B. Wang et al., 2016)(Azam, 2022). Drug delivery system is a combination of conventional drug delivery system with engineered technologies. Drug delivery system is a drug ability to be placed straight to the location of a target and the drug speed that is needed to be released is controlled (Sung & Kim, 2020). Biodegradable and bioresorbable properties of polymer sustainably develop various drug delivery systems. The rate of polymer degradation depends on crystallinity, chemical stability, hydrophobic/hydrophilic of polymer constituent elements, molecular weight distribution, fabrication process, particle size and porosity (Uskoković et al., 2022). One of the drug delivery systems examples is polymer material which is a hydrogel that is mostly used as a drug delivery system for its arrangeable, controlled degradability, and the ability to protect soluble drugs (Ciolacu et al., 2020; Li & Mooney, 2016; Sung & Kim, 2020).

Polymer Classification

A polymer is a macromolecule that contains repetition units covalently connected forming a long chain through a polymerization process (McKeen, 2016). Polymers can be classified into categories (Callister et al., 2007):

Based on the Polymerization Types

Addition Polymerization: A process in which monomer units are added one by one like a chain to create a linear macromolecule. During the addition polymerization, all monomers are used, and no side products are formed. The polymerization reaction happens in 3 phases i.e. chain initiation, chain propagation, and chain termination.

Condensation Polymerization: A polymer is formed through a gradual chemical reaction and is involved more than one monomer unit. On condensation polymerization, there is a release of a micromolecule as side products such as H₂O and HCl.

Based on the Resource

Natural Polymer: It may originate from animals or plants. For example sugar, protein, nucleotide, and lipid. It develops mostly for drug delivery systems cause its great biocompatibility on the in vivo examination (Hasnain et al., 2022).

Semi-synthetic Polymer: It is a modification of natural polymer through a chemical reaction. For example cellulose and vulcanized rubber.

Synthetic Polymer: An artificial polymer includes fiber and plastic that are used daily. In a drug delivery system, a used synthetic polymer can be biodegradable and non-biodegradable. Biodegradable synthetic polymers examples such as polyethylene glycol, polyester, polyamide, and polycaprolactone; and non-biodegradable synthetic polymers such as silicone (Srivastava et al., 2015).

Based on the Structure

Linear: a polymer with a straight chain structure with no branches

Branched: a linear polymer with an additional chain on its side and stick to the main chain

Cross-link/Network: a branch on the main chain connected to other chains

Based on the Respond to the Temperature Change

Thermoplastic: a thermoplastic polymer will soften and melt if it was heated and hardened if it was cooled. Because of this nature, this resin type can be injected into a mold or other mold techniques. This makes polymer also able to be re-processed/reused. Examples of thermoplastic polymers are polypropylene, polyester, polyether ether, polyether ether ketone, and polyoxymethylene (Hsissou et al., 2021).

Thermosetting: A thermosetting polymer chemically reacts to create a cross-linked structure that can limit the polymer chain movements. If heated, a polymer with this web structure tends to degrade rather than melt. Examples of thermosetting polymers are polyamide, polycarbonate, polyester phenolic, silicone, polyurethane, and polyepoxide (McKeen, 2016).

Polymer Types as A Drug Carriers

Both natural and synthetic polymers have been widely developed as a drug carriers (Foux & Zilberman, 2015). Some of these polymer types are used as a drug carriers, especially medicine that is used in periodontitis therapy, like gelatin, chitosan, cellulose, PLGA, and PLA (Wei et al., 2021).

Gelatin

Gelatin is a water-soluble polypeptide that can get from acid, base, or enzymatic hydrolysis from collagen which is the main protein component on skin, bones, and connective tissues (Foux & Zilberman, 2015). It is biocompatible, biodegradable, and not resulting in any negative response of immune systems (Foux & Zilberman, 2015). Gelatin is very soluble in water, thus, it needs to be cross-linked before being used in order to improve its mechanical properties, lowering its solubility and degradation. Cross-linking gelatin can be done physically by using microwave energy, biologically by enzymatic mechanism, and chemically by using materials such as formaldehyde, glutaraldehyde, glyceraldehyde, genipin, and carbodiimide. As the medicine-conducting system, gelatin can be a particle (micro and nanoparticle), fiber, and hydrogel (Foux & Zilberman, 2015). There are 2 types of gelatin in the market, A-type gelatin and B-type gelatin in which A-type gelatin is a cationic gelatin resulting from a part of acid hydrolysis of collagen while B-type is an anionic gelatin resulting from collagen base hydrolysis (Foux & Zilberman, 2015).

Chitosan

Among natural polymers, chitosan gains attention for its antimicrobe nature besides its high biocompatibility, non-toxic, and biodegradable natures. Chitosan is a polysaccharide that can get from chitin through a partial acetylated process at 60-80°C temperature using an alkali (Jafernik et al., 2023). The characteristics of chitosan and its application can be affected and determined by acetylated degrees and its molar mass (Garg et al., 2019)(Desai et al., 2023). The weakness of chitosan is its low mechanism and solubility natures in the physiologic pH environment condition, thus, to manipulate it, cross-linking is done or combining the chitosan with other polymers or used in a composite form (Lestari et al., 2022).

Cellulose

Cellulose is a polysaccharide consisting of a β -D-glucopyranose monomer and covers 3 hydroxyl groups for each anhydroglucose unit. Being developed in medicine-conducting systems for its good stability, high glass transition temperature (T_g), compatibility with various drug molecules, and most important nature its simplicity to formed micro or nano structure (Hasan et al., 2020; Kavitha et al., 2020). Cellulose is not well soluble in water or any other solution because the hydrogen ligament between

molecules is high (Kavitha et al., 2020). There are 2 cellulose groups i.e. ether cellulose (such as methyl, ethyl, hydroxyethyl, hydroxy ethyl methyl, hydroxypropyl, hydroxy propyl methyl, and carboxymethyl derivatives, and cellulose ester (cellulose acetate, acetate trimellitate, acetate phthalate, hydroxypropyl methyl phthalate, and hydroxypropyl methyl acetate succinate) (Kavitha et al., 2020).

PLGA

Poly(lactic-co-glycolic acid) or PLGA or PLG is a copolymer from polylactic acid (PLA) and Polyglycolic acid (PGA). The strength of PLGA is its physical properties that can be customized such as its molecule weight and lactic and glycolic ratios so it can be widely used as a medicine-conducting system, protein carrier, nucleic acid, peptide, and also a framework for tissue engineering (Han et al., 2016)(Yoo & Won, 2020)(Loureiro & Pereira, 2020). PLGA dissolves in various organic solvents like acetone, benzyl alcohol, chloroform, dichloromethane, ethyl acetate, hexafluoro isopropanol, and tetrahydrofuran (Сурья & Бхаттачарья, 2021). PLGA has a glass transition temperature between 40-60°C, depending on the copolymer composition and molecule weight (Kapoor et al., 2015)(Hines & Kaplan, 2013).

PLGA has 2 degradation types in the biology system i.e. hydrolysis and autocatalysis (Kapoor et al., 2015)(Hines & Kaplan, 2013). The monomer ratio is very important in hydrolysis degradation. Lactic ratio: a 50:50 glycolic acid has a faster degradation than an 85:15 lactic and glycolic acid ratio because lactic acid is hydrophobic (Kapoor et al., 2015)(Hines & Kaplan, 2013). The autocatalysis degradation happens in an acid environment (Kapoor et al., 2015)(Hines & Kaplan, 2013).

PLA

PLA is a polyester aliphatic hydrophobic that can originate from renewable sources such as wheat, corn, and rice so they can easily get it, the PLA application is very wide (Tyler et al., 2016). PLA dissolves in dioxane, acetonitrile, chloroform, methylene chloride, 1-1-2-trichloroethane, and dichloroacetic acid solutions; partly dissolves in ethyl benzene, toluene, acetone, and tetrahydrofuran (Vlachopoulos et al., 2022)(Casalini et al., 2019). The physical and degradation properties of PLA can be arranged by a combination of co-monomer hydroxyl acid components or by D- and L-isomer racemization. L-isomer on PLA creates PLLA which is a hard and transparent semi-crystalline polymer with a 45-70 MPa tensile strength value, while Poly (DL-lactide) (PDLA) is an amorphous polymer that doesn't have a melting point with a very low tensile strength value (Tyler et al., 2016).

Polymer Characteristics That Are Needed In the Drug Delivery System

Various types of polymers, natural, semi-synthetic, or synthetic are used in controlled medicine-conducting systems. The polymer that is used should have the requirements (Kost et al., 2000):

Safety: a toxic component (toxic impurities) should be removed from the polymer before being used like residual monomer, initiator, or other chemical materials that are used on synthetic polymer and modification.

Physical and Mechanism Properties: a polymer that is used should have physical and mechanical properties compatible with its usage and design dosage forms such as hardness, compressive strength, adhesivity, and cohesivity.

Biocompatibility: polymer doesn't cause significant local irritation effects on surrounding tissues. If it was biodegradable, the side product of the degradation process should be non-toxic, non-immunogenic, and non-carcinogenic.

Matrix Concepts in the Drug Delivery System

The matrix concept in a controlled drug delivery system is where the release of the drug done by continuously and controlled, both through dissolution and diffusion mechanisms. To control the release of the drug, which has a variety of solubilities, the drug disperse in a hydrophilic material (like hydroxypropyl cellulose, methylcellulose, starch, carboxymethyl chitosan, and sodium alginates), which can expand (swelling), or hydrophobic and non-dissolves materials (like wax, polyethylene, polypropylene, and ethylcellulose) (Abbas et al., 2019)(Akif, 2018). The technic of inserting drug (drug loading) into a polymer matrix are various, however, generally used are (Sabaa, 2016):

Solvent swelling technique: matrix is inserted into a highly concentrated drug solution and left to expand. The solvent is then removed through evaporation.

Supercritical fluid technique: a supercritical fluid (SCF) has a density like a general solution but low viscosity like gas. In this technique, a matrix is left to expand in a mixed drug solution and SCF. Then the SCF is easily removed by lowering pressure and leaving the drug contained in the matrix.

Direct compression method: drug is smashed and then mixed in the matrix with a binding material (binder) in a certain amount. Then compressed to form tablet with 2-3 ton/cm² pressure.

Polymer-Based Composite And Its Application In Periodontitis Therapy

A composite is a multiphase material that has different characteristics with each of its constituent components and is usually called a composite made (artificially made) with the purpose to gain material with a better properties and in accordance with its use (Callister et al., 2007). Generally, a composite material is made with only 2 phases. The first phase is a matrix or is used to call the continuity phase which covers the second phase called the dispersed phase or discontinuity phase (Li & Mooney, 2016). The matrix phase can be a metal, polymer, or ceramic (Callister et al., 2007).

A polymer-based composite has a polymer component as the matrix with one or more dispersed phases that can give enhancement to physical, chemical, and biological properties. A polymer-based composite can divide into two types based on the used filler i.e. bioactive polymer-based composite, which consists of bioactive filler or particle, and non-bioactive polymer-based composite, which consists of reinforcing or porogen fillers (Guo et al., 2021). The strength of polymer-based composite over metal and ceramic-based is the making process tends to be simple and inexpensive, and also able to create a complex structure material (Oladele et al., 2020). In general, polymer-based composite has an enhancement both in power or specific modules than single-element polymer material (Jiffrin et al., 2022).

Polymer-based Composite in Periodontitis Therapy

In periodontitis therapy, a polymer is used as a matrix to carry various drug materials such as antibiotics, antiinflammation, or acting substances in alveolar bones reparation and other periodontal tissues and there are some systems in conducting such as irrigation systems, strips, and films, fiber, gel system, and nano/microdrug delivery system as seen on image 1 (Wei et al., 2021). Those system do not require surgery in

their application, while membrane and scaffold system applied surgically (Steinberg & Friedman, 2020).

In its early development, the drug delivery system is made using non-biodegradable material and needs a removal of the therapeutic system at the end of the treatment (Zięba et al., 2020). This day, the drug delivery system in periodontitis therapy is mostly developed from natural polymers and has biodegradable characteristics (Zięba et al., 2020). As the benefit of this material usage is it doesn't need to another appointment (revisit) to remove it from inside of the periodontal pocket (Zięba et al., 2020).

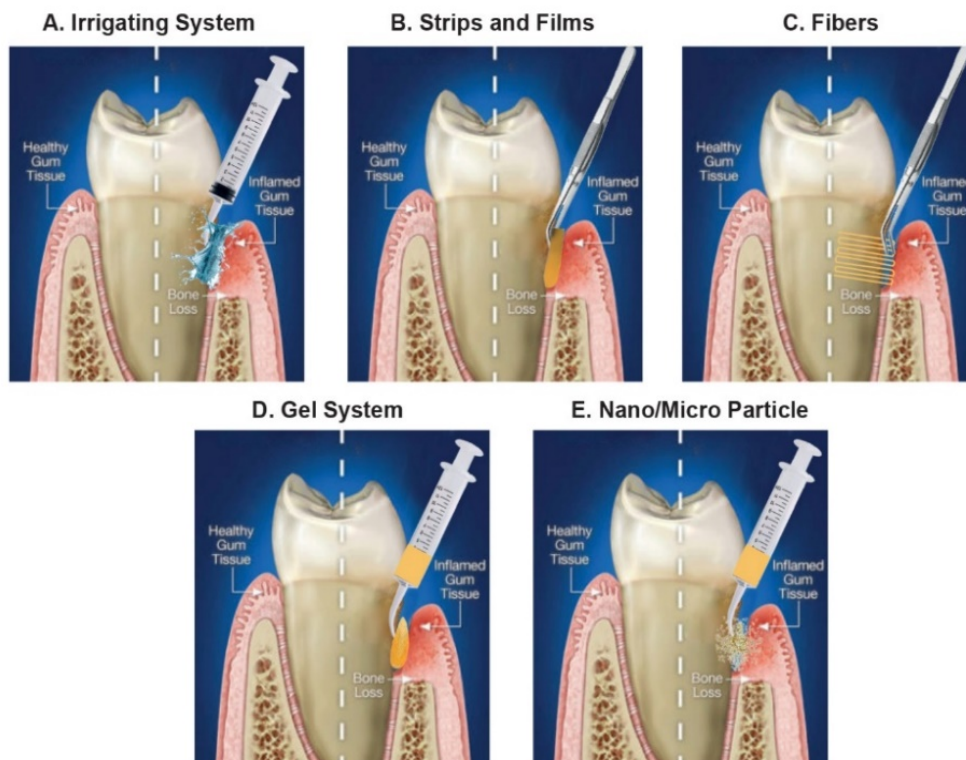


Figure 1. The illustration of the local drug delivery system in periodontitis therapy. The left side of each image is a condition of a healthy periodontal tissue, while the right side is an inflamed periodontal tissue. Various drug delivery system in periodontitis therapy that have existed and have been developed are as follows: A. Irrigation System; B. Strip and Film; C. Fiber; D. Gel System; and E. Nano/Micro-Particle System

Irrigation System

The irrigation system can easily eliminate bacteria in the pocket using a pressured solution. An example of this system is the combination of 0,6% triclosan, 1% of poly hexamethylene guanidine phosphate, 10% of povidone-iodine 0,25% of sodium hypochlorite, 0,75% of boric acid, and 20 mg/mL of zoned water that is proven decreasing the plaque index, bleeding index, periodontal pocket depth, and gum adhesion enhancement. In general, the irrigation system shows a better result significantly, however, the weakness of this system is the long effect term is invisible significantly, therefore, other types of medicine-conducting systems are developed, such as strip and film, fiber, gel, microspheres, and nanosystem.

Strips and Films

Strips and films are thin ribbon system matrices and the medicine is dispersed in it. The strength of the strip and film is its shape and size can be customized to the periodontal pocket and can be easily inserted, doesn't need an operator skill so it can be more convenient for patients and dentists. In the beginning, the strip and film are developed using acrylic material, however, this material has non-bioresorbable, non-degradable, and hard to take off causing an inflammation reaction. Other polymer types are developed such as poly-hydroxybutyric acid and polylactic-co-glycolic acid (PLGA) as the tetracycline carrier matrix. The strip and film with PLGA matrix that consists of 25% of tetracycline enable the release of the medicine up to 10 days after being inserted into the pocket and decrease bleeding incidents significantly in the event of probing.

A periochip is one of the strip and film products that has obtained FDA approval. A periochip is a gelatin polymer that brings chlorhexidine gluconate. The medicine release in a periochip can be seen after 7 days of being placed in the pocket.

Fiber

The fiber system is placed in the periodontal pocket circumferentially. Since 19893, fiber that consists of antibacterial material was being proposed. Goodson et al stated that tetracycline that is filled into acetate cellulose fiber can slow the microflora and has good biocompatibility (Steinberg & Friedman, 2020). This fiber system is less effective in controlling medicine concentration where 95% of the medicine is being released in the first 2 hours. Some polymers that are used as the matrix are poly (ε caprolactone), polyurethane, polypropylene, cellulose acetate propionate, and ethyl vinyl acetate.

The fiber system product ever circulating in the market and obtaining FDA approval is Actisite which is a fiber with a non-absorbable polymer consisting of tetracycline. Medical examination showed this product can keep the medicine concentration for up to 10 days after being placed in the pocket. Although Actisite showed a good medical examination clinical, this product was not too desirable because the application needed an operator's skill. Besides that, the patients didn't feel convenient after the fiber application and caused redness on the gum after the fiber was removed.

Gel System

This gel system has many strengths, some of which are easy to apply, uncomplicated making process, high biocompatibility, and its adhesive can enhance the medicine release efficiency without irritation or allergy effects. Polymers like Carbopol, carboxy methyl cellulose, and chitosan have been developed for this system. Chitosan is a polymer biodegradable combined with 15% of metronidazole has been proven effective in chronic periodontitis therapy.

Microspheres

Microspheres are polymers that have spheres/little oval shapes in 1-1000 μm size. A therapeutic agent is distributed uniformly on matrix polymer. A developed polymer can be biodegradable and non-biodegradable. A polymer that is developed using this microspheres system is microcapsule PLGA consisting of tetracycline. This microparticle system has good medicine release control and stability. A combination of PLGA and Poly ε caprolactone has been developed as the Doxycycline carrier, showing

a curative effect that can be seen after 3 months of in vivo examination. Other research showed the inserted Doxycycline in the microsphere system can maintain the concentration for up to 21 days and effectively slow down the growth of *P.gingivalis* and *F.Nucleatum*.

Arestin is a commercial product that adapts this system. Arestin has the PLGA component as a matrix consisting of antibiotic minocycline hydrochloride and has obtained FDA approval.

Nano-Delivery System

The nano-conducting system that has been developed recently are micelles, metal nanoparticle, nanoparticle polymer, and liposome. One of the strengths of this system is its ability to reach the unreachable place by a microparticle system because of its smaller size. This system also enhances the medical loading capacity so it can decrease the applied dosage. The metal nanoparticle is developed from silver, gold, and titanium related to its antimicrobial activity effects. Although it has a positive effect, the weakness of the metal nanoparticle is its toxicity and non-degradable which have been the attention of medical examination. Therefore, the polymer nanoparticle was developed. Yao et al have tested the polymer nanoparticle formulation consisting of minocycline with the diffusion-emulsification method as periodontitis therapy. Chitosan has also developed the polymer nanoparticle system. Xu et al develops chitosan consisting of doxycycline and show a good result in slowing the inflammation factor and *P.gingivalis* activity.

Research on polymer-based composites has been widely carried out and experienced very rapid development. Polymer-based composites for periodontitis therapy were first reported in 2002 by a group of college students from Fourth Military Medical University in Xian, China by combining macroporus nano hydroxyapatite/collagen and this study also an initial in the development of scaffold for alveolar bone regeneration. Currently, many studies have been conducted in developing polymer-based composites as periodontitis therapy. Lin et al, in 2020, combined silica on a nano-size Aurum Byspyramides surface and mix it on minocycline-loaded metacrylate gelatin (Lin et al., 2020). In the same year, Xu et al prepared a composite that an injectable sodium alginate based hydrogel system, combined with cubic cuprous oxide and polydopamine coated with titanium dioxide nanoparticles with the aim of overcoming the weakness of the membrane that cannot adapt to the size of the bone defect that occur (Xu et al., 2020). In addition, Wang et al, 2020, formulated drug-loaded PLGA microspheres into polyisocyanopeptide hydrogels (B. Wang et al., 2020). Not only placed directly in the periodontal poket, polymer based composite were developed as class V dental restorative materials which have function in inhibiting the development of periodontitis. This material contains ethoxylated bisphenol a dimethacrylate and pyromellitic dianhydrideglycerol dimethacrylate and dimethylaminohexadecyl metacrylate (L. Wang et al., 2016).

Conclusion

Periodontitis is a local infection; thus, the local medicine therapy and application is more efficient than the systemic medicine therapy that has a bigger side effect risk. Polymer-based composites with their broad variety enable the local drug delivery system included in periodontitis therapy and the good polymer is originate from nature or is synthetic after being developed as a matrix in the local drug delivery system.

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