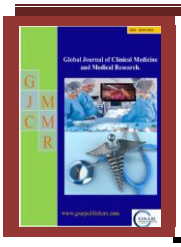

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NOVEL FRONTIERS ON LOCALIZED DRUG DELIVERY IN PERIODONTAL DISEASES: A CURRENT UPDATE

BY

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Abstract

As per the pharmacological and pathological study, Periodontitis is an inflammatory disease of the periodontium induced by specific microorganisms and requires more specific treatment. According to the National Institute of dental and Craniofacial Research shows overall, 42.2% of adults 30 years or older had total periodontitis, consisting of 7.8% with severe periodontitis and 34.4% with nonsevere periodontitis. The traditional mechanical therapy alone is not sufficient for the treatment of moderate to severe periodontitis because of in accessibility in the deep periodontal pocket and depth of penetration of microorganisms into the periodontal connective tissues. Thus to overcome the limitations of mechanical therapy, local drug delivery into the periodontal pocket is recommended. Periodontitis is seen worldwide in all groups of people. Various methods of treatments were used in the management of periodontal infection. The local drug delivery of chemotherapeutic agents to the periodontal lesion site has the advantage of loading a higher concentration of drug at the target site minimizing the adverse effect of the drug on the other systems of the body. The local drug delivery system having controlled release should be considered as an adjunctive to mechanical debridement for the treatment of periodontal diseases. There are various options of antimicrobials which can be locally delivered such as metronidazole, chlorhexidine, doxycycline, and tetracycline.

Keywords: *Antimicrobial agent, Controlled released, Chemotherapeutic agents, Periodontitis.*

1. INTRODUCTORY NOTES:

Periodontitis is defined as an inflammatory disease of supporting tissues of teeth initiated by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontium with periodontal pocket formation, gingival recession, or combination of both [1]. Periodontitis is multi factorial disease of periodontium initiated by periodontal pathogenic microorganisms and modified by the factors such as developmental deformities of the tooth, systemic conditions affecting oral tissues, environmental factors, socioeconomic factors, and stress. The nature of the periodontal disease depends on the interaction among the microorganisms, the oral environment, and the host's defence mechanisms to the bacterial assault, mainly composed of gram-negative anaerobic bacteria. This pathogenic micro biota occurs due to the accumulation of sub-gingival plaque. The current concept of treating periodontal diseases is based on eliminating oral bio films. A fundamental objective of periodontal therapy is to reduce or possibly eliminate the pathogenicity of the periodontal pathogenic microorganisms in the sub gingival periodontal area. There are two major approaches in periodontal therapy:

- To reduce or eliminate the total plaque micro flora by mechano therapy, such as scaling and root planing, to reduce or eliminate the specific pathogens in the subgingival plaque using antimicrobial agents as an adjunct to mechano therapy.
- The traditional treatment of periodontitis involves oral prophylaxis, which includes patient motivation, education regarding periodontal diseases, oral hygiene maintenance methods, professional mechanical debridement like scaling and root planing, air abrasive polishing system.

Mechanical debridement aimed at removing the Sub gingival micro flora and creating hard, clean, smooth, and compatible root surfaces. But in several conditions, the complex anatomy

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of the root and the location of the periodontal lesion may affect the ideal outcome of treatment and prevent the adequate reduction of the microbial load. The effectiveness of mechanical therapy is limited due to the lack of accessibility in deep periodontal pockets.[3] Putative pathogens associated with periodontal diseases are susceptible to a variety of antiseptics and antimicrobials [4-5]. Antimicrobials have been used as an adjunct with mechanical debridement in the management of periodontal infections. For the successful outcome of periodontal therapy, antimicrobial agents must reach beyond the depth of the periodontal pocket and produce gingival crevicular fluid concentration more than the Minimum Inhibitory Concentration (MIC) of the suspected periodontal microbes. Antimicrobial agents have been administered both systemically and locally. Systemic administration is usually indicated as an adjunct to scaling and root planning in order to prevent the re-colonization of pathogenic microorganisms. It is administered for a period of 7–14 days but it requires a higher concentration to be administered every few hours in order to stabilize the effective dose level. It may lead to adverse effects like hypersensitivity reaction, GIT disturbances, and bacterial resistance. These adverse effects would markedly be reduced if the antimicrobial agents are delivered locally into the periodontal pockets. Therefore local drug delivery used as an adjunct to scaling and root planing helps in the control of growth of pathogenic bacteria. The principle requirement for the effectiveness of local drug delivery is that the agent should reach at the base of the periodontal pocket and the concentration should be maintained at the site by means like a reservoir for an adequate time for the antimicrobial effect to occur. [1]

OBJECTIVE OF STUDY

The main objective of this review is to update the latest information regarding periodontal disease its symptoms available treatment, medication, latest technology, and futuristic approach for mitigation of problem.

HISTORICAL BACKGROUND

Dr. Max Goodson proposed the concept of controlled-release drug delivery in the treatment of periodontitis. He discussed the details of local drug delivery in the successful management of periodontal diseases. It's concluded that bacteria in mouth infect tissue surrounding the tooth leading to periodontal disease and other oral cavity problems:

- Bad breath or bad taste
- Red or swollen gums
- Tender or bleeding gums
- Painful chewing
- Gums that have pulled away from your teeth
- Loose teeth
- Sensitive teeth
- Any change in the fit of partial dentures

Ideal requisite of Locally Delivery Drug [4, 5, 7]

1. The drug delivery system should deliver the drug to the base of periodontal pocket.
2. Local drug delivery system should deliver drug at a microbiologically effective concentration.
3. Local drug delivery system should sustain the concentration of drugs in the pocket for sufficient time and concentration to be clinically effective.
4. It should retain at the proximity of periodontal pocket after placement.
5. It should be biodegradable& biocompatible.
6. It should not develop bacterial resistance.
7. The target dose should be sufficient enough to kill the targeted organisms also should not have any adverse effects.
8. It should not affect the commensally micro flora of periodontal pocket.
9. Drug must show *in-vitro* activity against the organisms.

Contraindication

Local drug delivery should not be used in the following conditions:

1. Periodontal patients with hypersensitivity reaction to any components of the Local Drug Delivery systems to be used.
2. As a replacement to scaling & root planning during initial periodontal therapy &maintenance.
3. In pregnant or lactating patients.
4. As a replacement for a surgical periodontal therapy in cases indicated for periodontal surgery.
5. As a replacement for systemic antibiotic therapy, where their systemic administration is indicated [6].

Advantages [4, 6]

1. Attains a 100-fold higher concentration of antimicrobial agents in sub-gingival sites.
2. The concentration of the drug in periodontal pocket is not affected by the fluctuation in plasma levels.
3. The technique is suitable for agents which cannot be given systemically, such as chlorhexidine
4. Small doses can be administered.
5. Super infection and drug resistance are rare.
6. Reduction in frequency of drug administration.

Disadvantages [4, 6]

1. Difficulty in placing into the deeper parts of the pockets of the furcation lesions.
2. Does not have any effect on adjacent or nearby structures such as tonsils, buccal mucosa act so may cause chances of re-infection.
3. Time consuming.
4. In presence of generalized pockets, other periodontal therapies should be used.

Classification [8, 9]

1. Langer & Peppas (1981) - Based on their mechanism of action.
   a. Diffusion-controlled systems.
   b. Chemically controlled systems.
   c. Solvent-activated systems.
   d. Release induced by external forces.
2. Kornman (1993)

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a. Reservoirs without a rate controlling system.
b. Reservoirs with a rate controlling system.

3. Rams and Slots (1996) - Based on application of therapy.

a. Personally applied.
i. Non-sustained sub-gingival drug delivery.
ii. Sustained sub-gingival drug delivery.

b. Professionally applied.
i. Non-sustained sub-gingival drug delivery.
ii. Sustained sub-gingival drug delivery.

4. SoskolneWa (1997) - Based on dosage form. a. Fibres e.g. Tetracycline. b. Films/slabs e.g. Chlorhexidine chip.
i. Non-degradable films
ii. Degradable film
iii. s c. Injectable systems e.g. Minocycline

5. Greenstein &Tonetti (2000) - Based on duration of action
a. Sustained release devices
b. Controlled release devices

6. Soskolone Wa Friedman M. - Depending on degradability:
a. Non-degradable devices
b. Biodegradable devices.

Various Drugs/Agents Used In the Local Drug Delivery System:

1. Tetracycline
2. Doxycycline
3. Minocycline
4. Metronidazole
5. Chlorhexidine

Other drugs like clarithromycin, Alendronates, ofloxacin, clindamycin.etc,

Tetracycline: Tetracycline has been widely used for the treatment of periodontal diseases. The Actisite tetracycline fibres have been approved both by the United States Food and Drug Administration (FDA) and by the European Union's regulatory agencies. These are non-resorbable, safe, inert copolymer loaded with 25% w/w tetracycline HCI. It maintains constant concentrations more than 1000 µg/mL for a period of 10 days. Follow-up showed reduction in the subgingival microbiota. Bioresorbable tetracycline fibre has been developed with base of collagen film, which is commercially available as Periodontal plus AB. It offers the advantage of no second appointment for removal as it degrades within 7 days. Tetracycline seratiopeptidase-containing gels were evaluated in a study by Maheshwari 2005. [7, 8, 9].

Fibers (actisite): These are non-resorbable biological inert, generally considered as safe, plastic copolymer (ethylene and vinyl-acetate) loaded with 25%w/w tetracycline HCL powder packaged as a thread of 0.5mm in diameter and 23cm in length. When packed into the periodontal pocket, it is well tolerated by oral tissues, and for 10 days it sustains tetracycline concentrations. Recently bio-resorbable tetracycline fibers have been developed with base of collagen films, which is commercially available as periodontal plus AB. It offers the advantage of no further appointment for removal as it biodegrades within 7 days [7, 9].

Gels: Tetracycline serratiopeptidase containing periodontal gel, the purpose was to reduce the polymer concentration and to obtain reasonable viscosity at a lower concentration of pluronic acid. Bio-erodible injectable poly for tetracycline-controlled delivery formulations loaded with tetracycline by 10% or 20% showed complete in vitro degeneration concomitant with drug release [2, 9].

Doxycycline: Doxycycline is a bacteriostatic agent. A biodegradable formulation containing; 10% by weight doxycycline, 33% by weight poly (DL-Lactide), and 57% by weight N- methyl 2-pyrrolidone. Approximately 95% of the polymer is bio-absorbed or expelled from the periodontal pocket naturally within 28 days. The efficiency of 10% doxycycline hyclate as a local delivery antimicrobial agent for achieving probing depth reduction and gaining clinical attachment shown in fig. It is a liquid biodegradable system that hardens when placed in the periodontal pocket [9, 8].

Minocycline: Minocycline HCL, a semi-synthetic tetracycline is one of the most active antibiotics for microorganisms associated with periodontitis. It has a significant antimicrobial activity against a wide range of organisms as well as an anti-collagenase effect [7]. There are three modes of local application are available;

1. Film
2. Microspheres
3. Ointment.

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 the drug, the fibres are secured by applying cyanoacrylate as an adhesive. [17]

Films: Film is a matrix delivery system where the drug is incorporated into the polymer, and it is released into the periodontal pocket by drug diffusion, erosion, or dissolution of matrix. This system is more commonly used for the delivery of drugs as it has several advantageous characteristics. The size and shape of the films are flexible it can be easily managed to adopt the periodontal dimensions to be treated. [17]

Preparation Methods for Films in Local Drug Delivery:

1. Solvent casting technique
2. Semisolid casting method
3. Hot-melt extrusion
4. Solid dispersion extrusion
5. Rolling method

Evaluation of Films in Local Drug Delivery:

1. Uniform thickness
2. Estimation of percentage moisture loss
3. Uniformity of weight
4. In-vitro drug release studies
5. Uniform drug content
6. Tensile strength

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7. Swelling index
8. Folding endurance
9. Surface pH
10. In-vitro antibacterial studies

Injectable systems: Injectable systems have an additional advantage of the easy and rapid application. Antimicrobial agents can directly be delivered using a syringe into the periodontal pocket without causing pain to the subject/ person. The cost and time taken for the therapy are 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 occupying more surface area of pocket and reaching to more pathogens.

Gels: Gels are semisolid mucoadhesive systems that have also received attention for the targeted delivery of antimicrobial agents. For instance, in terms of preparation and administration, they are easier. Gels have faster drug-releasing rates. Gels are applied sublingually using a blunt cannula or a syringe.

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.

Microspheres: A new, locally delivered, sustained release form of minocycline microspheres (arestin) for subgingival placement is available. The 2%minocycline is encapsulated into bio-resorbable microspheres in a gel carrier and has resorption time of 21 days. The gingival crevicular fluid hydrolyses the polymer and releases minocycline for a period of 14 days or longer before resorbing completely [8].

Ointment: The 2% minocycline hydrochloride in a matrix of hydroxyethyl-cellulose, amino alkylmethacrylate, triacetates& glycerine. The concentration of minocycline in the periodontal pocket is about 1300 µg/ml of gingival crevicular fluid, 1 h after single topical application of 0.05 mlointment, and is reduced to 90µg/ml after 7 h 27. It is available by the trade name dentomycin and periocline in European Union and Japan, respectively.

Metronidazole: Elyzol, is a topical medication containing an oil-based metronidazole25% dental gel, applied in viscous consistency to the periodontal pocket. Consists of 25% of metronidazole benzoate in a matrix consists of glyceryl monooleate and sesame oil. The gel is placed sub-gingivally with a syringe and a blunt cannula. The drug concentration is crevicular fluid follows an exponential pattern which is compatible with sustained drug delivery. Among the other antibiotics that have been considered for periodontal treatment, metronidazole has often been chosen because of its selective efficacy against obligate anaerobes. When metronidazole gel plus scaling and root planning were compared to root planning alone, the results have not been consistent. One investigation suggested that there was a better result over a 9-month observation period when combined therapy was employed for probing depth reduction [8, 10].

Chlorhexidine: Chlorhexidine belong to the family of biguanide, it is used as an antifungal and antibacterial agent. It is mainly active against gram-positive group of organisms. It is bacteriostatic at low and bactericidal at high concentrations. Chlorhexidine is being used in mouth rinses; chlorhexidine has only a short-lived effect on the pocket flora [7]. It is available in the forms of;

1. Mouth rinses
2. Gels
3. Varnishes
4. Chips.

Oxfloxacin: Oxfloxacin inserts pt-01 is a soluble insert, with both fast and sustained release parts containing 10% of ofloxacin and showed a constant drug level of above 2 mg/ml, (minimum MIC for most pathogenic organisms) which could be sustained for up to 7 days.The controlled release system exhibited a biphasic pattern with a rapid early release phase peaking at approximately 12µg/ml and stabilizing at approximately 2µg/ml from day 3 to 7 following insertion. According to Kinura initial investigations failed to any additional microbiological effect in a split-mouth design[12]. According to Yamagami, four weekly applications of the insert resulted in significant resolution of periodontal inflammation and improvement in other clinical parameters compared to control inflammation [13].

Periochip: A small chip composed of biodegradable hydrolysed gelatin matrix, comprised of 34% chlorhexidine cross-linked with glutaraldehyde and also containing glycerine and water. The chip is 5mm long, 4mm wide with 2.5mg of chlorhexidine gluconate. The chip releases chlorhexidine in vitro in a biphasic manner, initially releasing approximately 40% of the chlorhexidine within the first 24 hrs, and later releasing the remaining chlorhexidine in an almost linear fashion for 7-10 days [8].

Periocol-CG: It is prepared by incorporating 2.5mg chlorhexidine from a 20% chlorhexidine solution in collagen membrane. Size of the chip: 4 x 5 mm Thickness of the chip: 0.25-0.32mm Weight of the chips: 10mg wt. It has been shown that it resorbs after 30 days and their coronal edge degrades within 10 days [9].

Chlo-Site: It is an agent containing 1.5% chlorhexidine of xanthan type (Xanthan gel - saccharide polymer). The chlosite gel gets vanished from the pocket within 10 - 30 days of injection and effective concentration of chlorhexidine against microorganisms is established for at least 15days in the region. It stick inside the pockets and are not easily washed out by gingival fluid or saliva. It is very efficient in treatment of periodontal pocket and peri-implantitis [8, 10].

Satranidazole (SZ): It is another antibiotic that belongs to the 5-nitroimidazole group. SZ, (1-ethylsulphonyl-3-[1-methyl-5-nitro-2-imidazolyl]-2-imidazolidinone) is a novel nitroimidazole which differs from other 5-nitroimidazoles such as metronidazole, ornidazole, and tinidazole, in that 2 °C of the imidazole ring is connected through nitrogen to a substituted imidazolidinone. Satranidazole gel, when used as an adjunct with scaling and root planing in the management of

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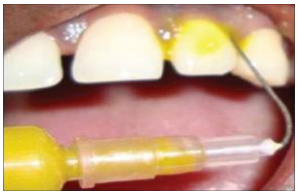
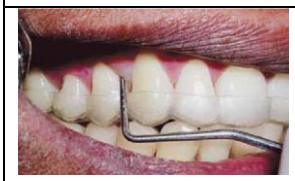
periodontitis, achieves significantly better clinical and microbiological results than mechanical periodontal treatment alone [11].

Various marketed formulations available[14, 15]

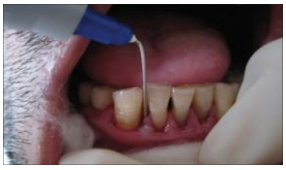
Agents	Product Available	Dosage form
Tetracycline	Actisite (25%w/v tetracycline Hcl) Periodontal plus AB(2mg of Tetracycline in 25mg of collagen	Non resorbable fiber Resorbable fiber
Doxycline	Atridox (10% Doxycycline)	Bio degradable mix in syringe.
Minocycline	Dentomycin gel (2% Minocycline) Arestin (2% Minocycline) Periocline (2.1%w/v Minocycline	Biodegradable gel Biodegradable Ointment
Metronidazole	Elyzol (25% Metronidazole)	Biodegradable gel
Chlorhexidine	Periochip (2.5mg Chlorhexidine) Periocol CG (2.5mg Chlorhexidine) Chlosite (1.5% Chlorhexidine	Biodegradable chip



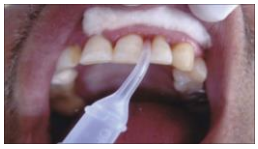
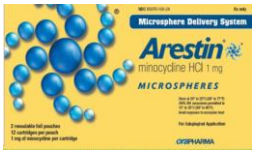

Tetracycline HCl



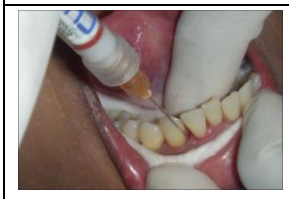

10% Doxycycline




25% Metronidazole

2% Minocycline




2.5 mg Chlorhexidine

12. LITERATURE REVIEW

Polak *et al;* 2012 examined that the appeared the impact of verbal diseases with P.*gingivalis*, F. *nucleatum*, or within the combination of both in periodontal tissues and concluded that the blended disease. (P.*gingivalis*, F.*nucleatum*) clearly come about in more damaging highlights than the mono-infections. Prove appears that the intelligent between distinctive bacterial species are vital components within the pathogenesis of periodontal illness. As in case F.*nucleatum*, situations around the teeth, the infusion of bacterial LPS, verbal gavage.

Molon R.S de *et al;* 2013 protrayed that periodontitis is an irresistible illness characterized by persistent inflammation of the periodontium, and its intervened and tweaked by the resistant framework. Within the nearness of micro-organisms or other antigens, resistant cells (macrophages/monocytes, dendritic cells, lymphocytes, neutrophills), endothelial cells, and fibroblasts discharge cytokines and trigger safe and inflammatory responses. In any case, when synthesized at all levels, cytokines alter the design of cellular response, partaking significantly within the improvement of constant inflammatory pathologies, such as periodontal disease. Understanding the origin and progression of bone resorption is one of the primary goals of the field of periodontics, aiming to arrest the disease progression and to optimize future treatments.

Mani *et al;* 2013 described that the periodontal disease is an infectious disease. Be that as it may, certain variables like natural, physical, and social and have stresses may influence and alter malady expression. Certain systemic clutters influencing the neurophil, monocyte/ macrophages and lymphocyte work result in charged generation or action of have incendiary arbiters which may influence the start and movement of gingivitis and periodontitis. Prove has moreover shed light on the banter side of relationship between systemic well-being and verbal well-being i.e. potential impacts of periodontal illness on a wide run of organ frameworks, just

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like cardiovascular, endocrine, regenerative and the respiratory framework.

Ramesh et *al*; 2016 study that periodontitis is an immune-inflammatory infection of the tissues encompassing the teeth. Different treatments modalities like mechanical debridement and utilize of antimicrobial have been taken after within treatment of such conditions. Presentation of neighborhood sedate conveyance framework within periodontal could be promising restorative methodology for accomplishing way better clinical results when utilized as an aide to customary non surgical periodontal therapy. Intensive research efforts are now focused on the development of new strategies for more effective treatment.

Rajpoot AS *et al*; 2017 examined that various antibacterial agents have been used effectively in the management of periodontal infection. The effectiveness of mechanical debridement of plaque and repeated topical and systemic administration of antibacterial agents are limited due to the lack of accessibility to periodontopathic organisms in the periodontal pocket. These products provide a long-term, effective treatment at the site of infection at much smaller doses. Prospective multicentre studies considering risk factors for disease progression have to be designed to identify patients who may benefit the most from local drug delivery.

Anarthe R *et al*; 2020 described that Periodontitis could be dangerous fiery infection of periodontium initiated by particular microorganisms and requires more specific treatment. The conventional mechanical treatment along is not adequate for the treatment of direct to extreme periodontitis since off in availability within the profound periodontal stash profundity of entrance of microorganism into the periodontal connective tissues. Thus to overcome the limitations of mechanical therapy, local drug delivery into the periodontal pocket is recommended. The local drug delivery of chemotherapeutic agents to the periodontal lesion site has the advantage of loading a higher concentration of drug at the target site minimizing the adverse effect of the drug on the other systems of the body. The local drug delivery system having controlled release should be considered as an adjunctive to mechanical debridement for the treatment of periodontal diseases.

Subramanian D *et al*; 2020 proposed that periodontitis is a fiery malady of strong tissues encompassing the teeth which is seen around the world in all bunches of individuals. Different strategies of medications were utilized within the administration of periodontal contamination. Various effective methods including mechanical debridement of plaque, topical and systemic administration of antibacterial agents in the treatment of such conditions. There are various options of antimicrobials which can be locally delivered such as metronidazole, chlorhexidine, doxycycline and tetracycline.

Pragati dubey *et al*; 2020 recommended that periodontal maladies comprises of a wide extend of inflammatory conditions which causes degeneration of periodontium and influences all supporting structure of teeth such as gingival, periodontal tendon, cementum, and alveolar bone, etc, taken after by teeth misfortune. WHO had detailed approximately 10-15% of world populace is enduring from extreme periodontal conditions. The pathophysiology of periodontal illness is related inside dental plaque, microbial biofilm course of action, and immunogenicity of the cell have. The reality of this ailment depends upon danger factors and chronological stages. Expectation is accomplished by day-by-day upkeep of verbal cleanliness. Distinctive surgical and non-surgical drugs are open to control the course of action of microbial biofilms. Ordinary bolster and periodic organization of the sickness control declining of conditions and shows up clear alter in verbal prosperity.

DISCUSSION AND CONCLUSION:

The review work suggested that the local drug delivery devices are a useful adjunct to conventional surgical or non-surgical periodontal therapy but are no substitute for these measures. Controlled-release delivery drug systems containing antibacterial, anti-inflammatory, antioxidant properties can be used effectively in the management of periodontitis. The local drug delivery provides a better improvement in periodontal conditions. Various chemical and herbal products are evaluated in local drug delivery systems with controlled release properties. It aims to minimize drug degradation and loss, prevent harmful adverse effects, and increase drug bioavailability at the site of the lesion. Though there are many studies conducted, there is insufficient comparative data to support any one of the local delivery systems as superior to another, and so further comparative studies are required to optimize the use of such local drug delivery systems in periodontal therapy.

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REFERENCES AND BIBLIOGRAPHY:

1. Newman MG, Takei H, Klokkevold PR, Carranza FA. Carranza's clinical periodontology. Elsevier health sciences; 2011; 14:234
2. Eija K, Mervi G, and Kahraman GU: Periodontitis Amultifaceted disease of tooth-supporting tissues. J of Clinical Medicine 2019; 8: 1135.
3. Mr. Prakash S, Dr. Biraju DP, Dr Dhaval VP, and Dr.Chetan HB: Recent advances in periodontal formulations. Int Journal of PharmaChem and Analysis 2014; 1: 69-80.
4. Magda F, Luciene CF, Geisla M, Silva S, and Marcelo F: Systemic antibiotics in the treatment of periodontitis. Periodontol 2000; 67(1): 131-86.
5. OiLeng Tan, Syarida Hasnur Safii and Masfueh Razali: Commercial local pharmacotherapeutics and adjunctive agents for nonsurgical treatment of periodontitis: A Contemporary Review of Clinical Efficacies and Challenges Antibiotics 2020; 9: 11

*Corresponding Author: **Manoj Kumar Katual**

6. Kalra S, Bathla S. Effect of Periodontal Diseases on Systemic Health. Periodontics Revisited. 2011:111.
7. Ramesh A, Prakash AP, Thomas B. Local Drug Delivery in periodontal diseases A Review. Journal of Health and Allied Sciences NU. 2016 Mar; 6(01):074-9.
8. Rajpoot AS, Parihar AS, Thakur S, Choudhary K, Rajput P, Chaudhary A. Local drug delivery in periodontics. Int J Res Health Allied Sci2017. 2017; 3:63-7.
9. Lacroix JM, Walker CB. Detection and incidence of the tetracycline resistance determinant tet (M) in the microflora associated with adult periodontitis. Journal of periodontology. 1995 Feb; 66(2):102-8.
10. Sugiarta AP, Lessang R, and Natalina: Effect of herbal toothpaste containing neem leaves extract (azadirachtaindica) against gingivitis: a clinical study. International Journal of Applied Pharmaceutics 2019; 11(1): 117-19.
11. Kimura S, Toda H, Shimabukuro Y, Kitamura M, Fujimoto N, Miki Y, Okada H. Topical chemotherapy in human periodontitis using a new controlled-release inserts containing ofloxacin. I. Microbiological observation. J Periodontal Res. 1991 Jan;26(1):33-41
12. Yamagami H, Takamori A, Sakamoto T, Okada H. Intrapocket chemotherapy in adult periodontitis using a new controlled-release insert containing ofloxacin (PT-01). J Periodontal. 1992 Jan; 63(1):2-6
13. Dodwad V, Vaish S, Mahajan A, Chhokra M. Local drug delivery in periodontics: a strategic intervention. International Journal of Pharmacy and Pharmaceutical Sciences.2004; 4(4):30-4.
14. Baiju CS, Manchanda S. Chair side therapeutic aids in periodontics. Heal talk. Nov-Dec 2010; 3(2):41-2.
15. Polak, David, et al. "Mouse model of experimental periodontitis induced by Porphyromonas gingivalis/ Fusobacterium nucleatum infection: bone loss and host response." Journal of Clinical Periodontology 36.5 (2012): 406-410.
16. de Molon RS, de Avila ED, Cirelli JA. Host responses induced by different animal models of periodontal disease: a literature review. Journal of investigative and clinical dentistry. 2013 Nov; 4(4):211-8.
17. Ramesh, A., Prakash, A. P., & Thomas, B. (2016). Local Drug Delivery in Periodontal Diseases. A Review. Journal of Health and Allied Sciences NU, 6(01), 074-079.
18. Anarth R, Kale P, Mani A and Kendre S: Local drug delivery in periodontitis: an innovative treatment modality. Int J Pharm Sci & Res2021; 12(9): 4616-25.
19. Subramaniam, D. D. Local Drug Delivery in Periodontics-A Review. European Journal of Molecular & Clinical Medicine, 7(08), 2020 1874-1881.
20. Pragati S, Ashok S., Kuldeep S. Recent advances in periodontal drug delivery systems, International Journal of Drug Delivery, 2009 1-14.

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