IJPSR (2021), Volume 12, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 14 June 2020; received in revised form, 27 January 2021; accepted, 21 May 2021; published 01 September 2021

LOCAL DRUG DELIVERY IN PERIODONTITIS: AN INNOVATIVE TREATMENT MODALITY

Raju Anarthe *, Preeti Kale, Amit Mani and Shriram Kendre

Department of Periodontology, Rural Dental College of Pravara Institute of Medical Sciences- DU Ahmednagar Loni - 413736, Maharashtra, India.

Keywords:

Antimicrobial agents, Chronic Periodontitis, Controlled release, Sustained release

Correspondence to Author:
Dr. Raju Anarthe

Department of Periodontology, Rural Dental College of Pravara Institute of Medical Sciences- DU Ahmednagar Loni - 413736, Maharashtra, India.

E-mail: rajuanarthe@gmail.com

ABSTRACT: Periodontitis is a destructive inflammatory disease of the periodontium induced by specific microorganisms and requires more specific treatment. 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. 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. This article reviews local drug delivery systems containing antimicrobial agents. Further extensive comparative studies are required to optimize the use of novel drugs in the local drug delivery system to manage periodontal diseases.

INTRODUCTION: 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 a 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.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(9).4616-25

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(9).4616-25

The nature of the periodontal disease depends on the interaction among the microorganisms, the oral environment, and the host's defense mechanisms to the bacterial assault, mainly composed of gram-negative anaerobic bacteria [2]. This pathogenic microbiota occurs due to the accumulation of subgingival plaque. The current concept of treating periodontal diseases is based on eliminating oral biofilms. A fundamental objective of periodontal therapy is to reduce or possibly eliminate the patho genicity of the periodontal pathogenic microorganisms in the subgingival periodontal area. Theoretically, there are two approaches in periodontal therapy:

To reduce or eliminate the total plaque microflora by mechno 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 suprgingival and subgingival microflora and creating hard, clean, smooth and compatible root surfaces. But in several conditions, the complex anatomy 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 recolonization 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 [6]. It was in the year 1979 when Dr. Max Goodson *et al.* [7]. first proposed the concept of controlled release drug delivery in the treatment of periodontitis. This review discusses the details of local drug delivery in the successful management of periodontal diseases.

Classification of Local Drug Delivery: Various classification systems of local drug delivery systems were evolved.

A Based on the Application Rams and Slots [8] 1996:

- Personally applied (Patient self-care application)
- Nonsustained subgingival drug delivery
- Home oral irrigation
- Home oral irrigation jet tips
- Traditional jet tips
- Oral irrigation (water pick)
- Soft cone rubber tips (Pickpocket)
- Sustained subgingival drug delivery

Professionally Applied in Dental Office:

- Nonsustained subgingival drug delivery
- Professional pocket irrigation
- Sustained subgingival drug delivery
- Controlled release devices
- Hollow fibers
- Dialysis tubing
- Strips
- Films

B Based on the Duration of Medicament Release Greenstein and Tonetti 2000 [8]:

- Sustained release devices
- these devices provide drug delivery for less than 24 h
- require multiple applications
- follow first-order drug kinetics
- Controlled release devices
- drug release is for more than 24 h
- administered only once

- follow zero-order drug kinetics

C Depending on degradability [9]:

- Non-degradable devices (First generation)
- Degradable devices (Second generation)

D Langer and Peppas [10] 1989: Classified controlled drug release polymeric systems based on their mechanism of action.

- Diffusion Controlled Systems
- Matrices
- Reservoirs
- 2. Chemically Controlled Systems
- Erodible systems
- Pendant chain systems
- 3. Solvent Activated Systems
- Osmotic systems
- Swelling controlled systems
- 4. Release Induced by External Forces

E Kornman [11] (1993) has Classified the Controlled Release Local Drug Delivery System as:

- Reservoirs without a rate controlling system like hollow fibers, gels and dialysis tubing.
- Reservoirs with a rate controlling system like erodible polymeric matrices, micro-porous polymer membrane, monolithic matrices and coated drug particles.

F Depending on the Origin:

- Allopathic or chemical local drug delivery
- Herbal or ayurvedic local drug delivery

G According to WHO Guidelines, Herbal Medicines Can Be Categorized Into Four Categories [12]: Based on their evolution, origin, and forms of current usage as under:-

Category 1: These indigenous herbal medicines are used by local communities or region and are very well-known by the local population through ages in context to composition, treatment, and dosage.

Category 2: This group consists of herbal medicines in systems and is well-documented and based on long-time usage on theories and concepts that are duly accepted by the respective countries. Example – Ayurveda Siddha and Unani.

Category 3: This consists of Modified herbal medicines which have been modified in relation to their shape, dose, administration mode, and composition. These medicines have to meet the national regulatory requirements in terms of their safety and efficacy.

Category 4: Imported products with a herbal medicine base include all the imported herbal medicines (raw materials and products). The national authority of the importing country should have safety and efficacy data.

H Based on the Types of Local Drug Delivery System [13]:

- Fibers
- Films
- Strips
- Gels
- Vesicular liposomal systems
- Microparticle systems
- Nanoparticle systems

Indications for Local Drug Delivery [14]:

- Localized periodontal pockets with probing pocket depth >5mm, after completion of successful phase I therapy,
- Medically compromised patients where surgical therapy is contraindicated or not suggested,
- As an adjunct to mechanical debridement,
- In patients suffering from recurrent or refractory periodontitis,

Where periodontal surgery is contraindicated, and the patient is on supportive periodontal treatment, Contraindications of Local Drug Delivery [14]:

- Patients with known hypersensitivity to the antimicrobials used,
- Patients susceptible to bacterial endocarditis who are contraindicated for subgingival irrigation devices to avoid the risk of bacterimia,

- Delivery of antimicrobials using ultrasonic devices is contraindicated in asthmatics, infective conditions such as AIDS, tuberculosis and those with cardiac pacemakers.
- In pregnant and lactating mothers where use of the particular antimicrobial are to be avoided.

Advantages of Local Drug Delivery [15]:

- Improved patient compliance.
- Improved pharmacokinetics.
- Improved drug access to the site of disease.
- Lowers the total drug dosage.
- No risk of emergence of resistant microorganism.
- Drug can reach the site of action in adequate concentration.
- Maintain the drug level for a sufficient period of time.

Disadvantage of Local Drug Delivery [15]:

1. Time-consuming and laborious
2. Difficulty in placing therapeutic concentration of antimicrobial agent into deeper periodontal pockets and furcation lesions
3. Personal application of antimicrobial agents by patients as a part of their home self-care procedure is compromised.

Potential Limitations Are: If used as a monotherapy, there could be a possibility of inability to disrupt biofilms, allergic reactions, and failure to remove local factors.

With the existing systems, concerns have been raised regarding the drug release rate, which might be more rapid than anticipated, or the poor biodegradability of the polymer.

Pharmacokinetic Parameters Criteria for Local Application [16]:

Site of Action: Local drug delivery targets microbiota deep into the connective tissue of periodontal pocket altered and exposed cementum of radicular dentin.

Reaching the drug to the entire surface area of the periodontal pocket is also difficult due to its small entrance. Thus local drug delivery is not used as monotherapy and is always done as an adjunct to SRP. Moreover, Anatomic anomalies, deep pockets, and furcation lesions may also impart physical difficulty in delivering the drug at the indicated site, thereby further impeding the drug efficacy at the local site.

Adequate Concentration: It has been proved by various experimental studies that the minimum inhibitory concentrations of antimicrobial agents should be at least 50 times higher than for bacteria growing under planktonic conditions. It is ensuring adequate drug concentration and enhancing its efficacy at the local site subgingivally.

Sufficient Duration: Duration of action of the local drug delivery agent is dependent upon the mechanism by which the antimicrobial agent inhibits or destroys target bacteria, bactericidal or bacteriostatic pathway. So an adequate drug-microbial interaction time must be attained for an antimicrobial agent to act against targeted microorganisms.

Substantivity: Substantivity refers to the property of an antimicrobial to bind or adsorb to soft and/or hard tissue lining of the periodontal pocket, thereby establishing a drug reservoir at the local site. Based on, an assumed pocket volume of 0.5 cuml and a gingival crevicular fluid flow rate of 20µl /h, it was estimated that half-life of a drug delivered into a periodontal pocket is about a minute. Therefore the addition of local drug delivery agents into various vehicles or devices prior to placement into the periodontal pocket enhances its substantivity.

Ideal requisite of Locally Delivery System [7]:

- Local drug delivery system should deliver drug to the connective tissue apically and laterally of the periodontal pocket.
- Local drug delivery system should deliver drug at a microbiologically effective concentration.
- Local drug delivery system should sustain the concentration of drugs in the pocket for sufficient time and concentration to be clinically effective.

- It should be easy to deliver into the periodontal pocket.
- It should retain at the proximity of periodontal pocket after placement.
- It should be biodegradable.
- It should not develop bacterial resistance.
- It should be safe without any adverse effects.
- It should not affect the commensal microflora of periodontal pocket.

According to Liechty *et al.*, the Drug Can Follow one of the Following Mechanism for Controlled Release [17].

- Desorption of surface-bound/ adsorbed drugs
- Diffussion through the carrier matrix
- Diffusion (in the case of nanocapsules) through the carrier wall
- Carrier matrix erosion
- Combined erosion/diffusion process

The efficacy of a drug delivery system is mainly affected by the biological environment and the properties of the polymer and the drug [18]. The mode of delivery primarily controls the drug success and failure.

Various Local Drug Delivery Systems: Locally delivered drug is formulated by inserting them into a vehicle in the form of fibers, gels, strips, among others to improve its bioavailability at the site. Most probably, the drug should have a resorbable vehicle so that there is no need to remove the vehicle after insertion [19].

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.

Films: Film is a matrix delivery system where the drug is incorporated into the polymer, and it is released into the periodontal pocket by either 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.

Preparation Methods for Films in Local Drug Delivery [20]:

- Solvent casting technique
- Semisolid casting method
- Hot-melt extrusion
- Solid dispersion extrusion
- Rolling method

Evaluation of Films In Local Drug Delivery [21]:

- Uniform thickness
- Estimation of percentage moisture loss
- Uniformity of weight
- *In-vitro* drug release studies
- Unifom drug content
- Tensile strength
- Swelling index
- Folding endurance
- Surface Ph
- *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.

Vesicular Liposomal Systems: Vesicular liposomal systems are investigated intently in order to be used as local drug delivery in periodontal diseases. This is because they are designed to mimic the bio-membranes in terms of structure and their behaviour.

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 include natural polymers, modified natural substances, and synthetics.

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 results in a decreased frequency of administration, and it also provides a more uniform distribution of the drug.

Chemical Agent Used In Local Drug Delivery: Tetracycline:- These are broad-spectrum antibiotics that are more effective against gram-positive bacteria. Tetracycline is a bacteriostatic antibiotic that interferes with bacterial protein synthesis and inhibits tissue collagenase activity. Tetracycline achieves 2 to 10 times more concen-trated in gingival crevicular fluid than the concentration in the serum. Tetracycline is available as biodegradable and non-biodegradable form for the local drug delivery system.

Actisite: Actisite was the first commercial lised, controlled-release antimicrobial local drug delivery product introduced in 1994. It is 23 cm long with 0.55 mm diameter, delivering 12.7 mg of tetracycline hydrochloride. The fibre is non-biodegradable and has to be retrieved after 10 days which is the disadvantage of this system. Actisite achieves a concentration of 1590 μg/ml of gingival crevicular fluid in the periodontal pocket however, 250 mg of oral tetracycline achieves a concentration of 1 μg/ml in the gingival crevicular fluid. The concentration level remained at a mean of 1300 μg/ml for 7 days in local drug delivery of Actisite [22].

Periodontal Plus AB: It biodegrades within 7 days, so there is no need for a second appointment. Collagen fibril-based formulation contains tetracycline hydrochloride (2 mg of tetracycline) in which 25 mg are collagen fibrils that can be directly applied for all levels of periodontal infections [23]. Kataria *et al.* [24]. applied tetracycline fibers as an adjunct to scaling and root planing and found it to be more effective in reducing gingival and periodontal inflammation (P=>0.05). A Tetracycline-Serratiopeptidase- A combination gel of tetracycline and serratiopeptidase was investigated by Maheshwari [25] *et al.*, observed that formulation had shown statistically significant results along with mechanical debridement. Sachdeva and Agarwal [26] made tetracycline in the form of a modified collagen matrix and used along with scaling and root planing. They concluded that there was significant probing pocket depth reduction and gain in clinical attachment for the SRP and tetracycline group compared to SRP alone.

Minocycline: It is a broad-spectrum antibiotic that is a derivative of tetracycline. It exhibits bacteriostatic action. It has greater substantivity and lipid solubility than tetracycline. It is available in various forms such as film, microspheres, ointment, and gel.

Film: Ethylcellulose film with 30% minocycline is used as a sustained-release device drug delivery system.

Microsphere: FDA has approved sustained-release minocycline microspheres as a local drug delivery system. It is commercially available by trade name as ARESTIN. ARESTIN is a 2% minocycline encapsulated into bio-resorbable microspheres with 20-60μm diameter in a gel carrier and it has a resorption time of 21 days.

Ointment: The 2% minocycline hydrochloride in a matrix of hydroxyethyl-cellulose, amino alkyl-methacrylate, triacetine & 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 ml

ointment 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.

Doxycycline: Doxycycline is a bacteriostatic agent. Its effective against the matrix metalloproteinase (MMP's) and has the ability to down-regulate matrix metalloproteinase (MMP's) [28]. MMP's are the periodontal biomarkers causing the destruction of periodontal connective tissue. ATRIDOX (42.5 mg Doxycycline) is the only subgingival controlled-release local drug delivery system, a commercially available product of doxycycline composed of a two syringe mixing system. It is the only FDA-approved 10% Doxycycline gel accepted by ADA. Doxycycline levels in GCF peaked to 1,500 - 2000 μg/ml of GCF in 2 h following the delivery of ATRIDOX. Local levels of Doxycycline have been found to remain well above the MIC for periodontal pathogens (6.0 μg/ml) for the 7 days. Within 28 days the 95% of the polymer of ATRIDOX is bio absorbed or expelled from the periodontal pocket [29].

Chlorhexidine: It is an anti-fungal and anti-bacterial agents, available as mouth rinses, gels, varnishes, and chips. Rolla and Melsen [30] reported that it acts by binding to anionic acid groups on salivary glycoproteins, thus reducing pellicle formation and colonization of microorganisms in the plaque. Chlorhexidine has been shown to be an effective agent with higher substantivity. It has greater affinity for hydroxyapetite and acidic salivary protein. Due to increased cellular membrane permeability and ability to induce the coagulation of intracellular cytoplasm macro-molecule it is effective as an antibacterial agent.

Periochip: It is a baby nail-sized chip composed of biodegradable hydrolyzed gelatin matrix, cross-linked with glutaraldehyde containing glycerine & water. The dimension of periochip is 4 × 5 × 0.35 mm with an available concentration of chlorhexidine 2.5 mg. *In-vitro* study, it is evaluated that periochip releases chlorhexidine in a biphasic manner, initially releasing approximately 40% of the chlorhexidine within the first 24 h and then releasing the remaining chlorhexidine in linear fashion for 7–10 days [30]. One border of periochip is rounded which is directed apically while inserting into the periodontal pocket to avoid mechanical trauma to the sulcular and junctional epithelium.

Periocol-CG: Periocol CG is also a chlorhexidine chip with a dimension of 4 × 5 × 0.25 to 0.32 mm prepared by incorporating 2.5 mg chlorhexidine from a 20% chlorhexidine solution in a collagen membrane. The weight of Periocol CG is 10 mg [31].

Chlo-Site: It is an agent containing 1.5% chlorhexidine in xanthan type. Xanthan gel is a saccharide polymer, which constitutes of a three-dimensional mesh mechanism, which is biocompatible with chlorhexidine [32].

Metronidazole: It is a nitroimidazole compound. It is bacteriocidal to anaerobic organism. It acts by disrupting bacterial DNA synthesis. After delivery of Elyzol (25% Metronidazole), concentrations of above 100 μg/ml of drug in GCF were measurable in the periodontal pocket for at least 8 h, and concentrations above 1 μ/ml were found after 36 h. It is delivered in viscous consistency to the pocket, where it is liquidized by the body heat and then hardens again, and forming crystals in contact with GCF or saliva [33].

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 periodontitis, achieves significantly better clinical and microbiological results than mechanical periodontal treatment alone [34].

Herbal Agents Used In Local Durg Delivery: Recently, usage of the herbal product has increased because of the relatively safe nature of herbal extracts; many herbal products and their components are being used for treating periodontitis in the form of local drugs delivery.

Neem: Neem leaf extract can help reduce bacterial load in dental plaque levels that cause the initiation and progression of periodontitis. It is evaluated that

bioactive materials available in neem leads to the presence of gallotannins during the early stages of plaque formation that could effectively reduce the bacterial load in dental plaque and help removal of plaque from the tooth surface and oral cavity through the aggregate formation. Additionally, the effective inhibition of glucosyl transferase activity and the reduced bacterial adhesion to saliva-coated hydroxyl appetite suggest some potential anti-plaque activity [35].

Aloe vera: *Aloe vera* is the commonly used medicinal cactus plant that belongs to the Liliaceae family. More than 300 species of aloe plants exist in the world, but only two species have been studied for local drug delivery, which are Aloe barbadensis Miller and Aloe arborescence. *Aloe vera* is having anti-inflammatory, antibacterial, antioxidant, antiviral, and antifungal actions as well as producing hypoglycemic effects.

It is effective in reducing gingival bleeding, inflammation, and swelling. It is a powerful healing promoter and can be used following tooth extractions also [36].

Lemon Grass: It is a popular medicinal plant. This plant is commonly used in teas, cosmetics, and folk medicine for its antiseptic, antiemetic, anti-rheumatic, analgesic, antispasmodic, and antipyretic properties.

Its chemical components like phenol and flavanoid substances were reported to show many *in-vitro* and *in-vivo* biological activities such as antioxidant, anti-inflammatory, and anti-mutagenic activities. At a concentration of 2% lemongrass, essential oil appears to be an effective local drug delivery agent as an adjunct to mechanical nonsurgical periodontal therapy [37].

Green Tea: Green tea is an effective local drug delivery agent as it contains a number of bioactive chemicals such as flavonoids, including catechins and their derivatives. Green tea is rich in therapeutic effects such as antioxidant, anti-collagenase, anti-inflammatory, anti-caries, anti-fungal, antiviral and antibacterial effects. Mageed MJ *et al* [38]. investigated the antimicrobial effects of green tea extracts on Porphyromonas gingivalis, and he found that alcoholic green tea extract was able to inhibit Porphyromonas gingivalis.

Tea Tree Oil: Tea tree oil (TTO) is derived from the paperbark tea tree.TTO has a broad-spectrum antimicrobial, antifungal, antiviral, antioxidant, and anti-inflammatory effect. Elgendy EA39 suggested that TTO is effective as an adjunctive treatment of scaling and root planing on the clinical parameters.

Curcumin: Turmeric (Curcuma longa) is an Indian spice derived from the rhizomes, a perennial member of the Zingiberaceae family. Turmeric is rich in curcuminoids such as curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxy curcumin as well as volatile oils (turmerone, atlantone, and zingiberene), sugars, proteins, and resins. Curcumin exhibits anti-inflammatory, antioxidant, anticarcinogenic, antiviral, and antimicrobial activities. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2, lipoxygenase, and inducible nitric oxide synthase enzymes and inhibits the production of the inflammatory cytokines [40].

Oak: Oak is a species from the Fagacea family, which is grown in Western Iran. Oak is rich in hemostatic, anti-bacterial, anti-inflammatory, anti-nociceptive, and anti-oxidant effects and has been traditionally used for the treatment of gastric ulcers, superficial injuries, and local inflammation. Oak has been evaluated as a local drug delivery agent in periodontal diseases [41].

Coriander: Coriander Sativumis from the Umbelliferae family was used in Iranian folk medicine as a carminative and spasmolytic agent. It is effective local drug delivery agent as it has anti-inflammatory, analgesic, anti-bacterial and anti-oxidant activities. *C. sativum* extract has tannins also. Yaghini J [41]. conducted a randomized, double-blinded controlled trial to evaluate the clinical effects of subgingival application of herbal gel (extracts of oak and coriander) in periodontal pockets. Results showed statistically significant improvements in periodontal indices (P=<0.05).

Babul: Babul has cyanogenic glycosides in addition to several enzymes such as oxidases, peroxidases, and pectinases that have shown to inhibit microbial growth. Its bark contains tannins (24-42%) which have analgesic, anti-inflammatory properties [42].

Rameshwari Singhal 43 *et al.* suggest the action of acacia gum against suspected periodontal pathogens like Actino bacillus action mycete mcomitans, Capnocytophaga spp., Porphyro-monasgingivalis, Prevotella intermedia and c and their enzymes have a clinical value.

Bakul: One of the major pharmacologically active ingredients lupeol is present in bakul has anti-inflammatory and anti-microbial properties, which has attracted the researchers' attention towards Bakul for scientific studies [43].

Pomegranate: Pomegranate has active compounds containing polyphenolic flavonoids (e.g. Punicalagins and ellagic acid) are believed to prevent gingivitis through a number of mechanisms, including reduction of oxidative stress in the oral cavity, antioxidant activity, anti-inflammatory effects and anti-bacterial effects, so rinsing with pomegranate lowers the activity of alfa glucuronidase, an enzyme that breaks down sucrose while it increased the activities of ceruloplasmin, an antioxidant enzyme. Gomes LA44 (2016) did a study to evaluate the antimicrobial activity of pomegranate glycolic extract (PGE) against the periodontal pathogen Porphyromonas gingivalis by using Galleria mellonellaas *in-vivo* model and results were significant.

CONCLUSION: The review of studies 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, anti-oxidant 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.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

ACKNOWLEDGMENT: Nil

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Newman, MG, Carranza FA, Takei H and Lokkevold K: Carranzas Clinical Periodontology. Elsevier Health Science 13th 2018.
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 Pharma Chem 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. Oi Leng 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.
6. Rajesh H, Vinita AB, Anupama SR, Sruthy P and Haziel JD: Journal of Global Bio Sciences 2014: 3(6); 904-09.
7. Amitha R, Agumbe PP and Biju T: Local drug delivery in periodontal diseases: A Rev NUJHS 2016; (6)1: 2249-10.
8. Rams TE and Slots J: Local delivery of antimicrobial agents in the periodontal pocket. Periodontol 2000; 1996; 10; 139-59.
9. Divya PV and Nandakumar K: Local drug delivery periocol in periodontics. Artif Organs 2010; 19(2): 74-80.
10. Langer R and Peppas NA: Advances in biomaterials, drug. Delivery and Bio Tech AI ChE J 2003; 49(12): 2990-06.
11. Kornman KS: Controlled-release local delivery antimicrobials in periodontics: prospects for the future. J Periodontol 1993; 64: 782-91
12. Gupta R, Ingle NA, Kaur N, Yadav P, Ingle E and Charania Z: Ayurveda in dentistry a review. J Int Oral Health 2015; 7(8): 141-3.
13. Dr Vidya D, Dr Shubhra V, Dr Aakriti M and Dr Mehak C: Local drug delivery in periodontics: a strategic intervention. Int J Pharm Pharm Sci 2012; 4: 30-34.
14. Puri K and Puri N: J of Medi and Life 2013; 4: 414-19.
15. Chadha VS, Arora K, Manjunath BC and Kalra S: Local drug delivery in periodontics: Current concepts and trends. Int J Adv Res Ora Sci 2012; 1(1): 1-9.
16. American Academy of Periodontology Statement on Local Delivery of Sustained or Controlled Release Antimicrobials as Adjunctive Therapy in the Treatment of Periodontitis. J Periodontol 2006; 77(8): 1458-58.
17. Liechty WB, Kryscio DR, Slaughter BV and Peppas NA: Polymers for drug delivery systems. Annu Rev Chem Biomol Eng 2010; 1: 149-73.
18. Bruschi ML and DE Freitas O: Oral bio adhesive drug delivery systems. Drug Dev Ind Pharm 2005; 31: 293-10.
19. Dk Siti Najwa Rashidah Pg Hj Ismail, Rajan Rajabalaya, Sheba R David and Jagjit Singh Dhaliwal: journal of dental and maxillofacial research current status of local drug delivery sytems in the treatmnet of periodontal diseases. J Dent Maxillofacial Res 2019; 2(3): 2-5.

20. Jain N, Jain GK, Javed S, Iqbal Z, Talegaonkar S, Ahmad FJ and Khar RK: Recent approaches for the treatment of periodontitis. Drug Discovery Today 2008 13: 932-43.
21. Jyoti P, Ila T, Guljot S, Fatima T, Anuj SP and Neha K: Journal of International Oral Health 2016; 8(2): 296-01.
22. Vyas SP, Sihorkar V and Mishra V: Controlled and targeted drug delivery strategies towards Intra periodontal pocket disease. J Clin Pharm Ther 2000; 25(1): 21-42.
23. Kataria S, Chandrashekar KT, Mishra R, Tripathi V and Galav A: Effect of tetracycline HCL (Periodontal plus AB) on Aggregati bacter actinomycetemcomitans levels in chronic periodontitis. Arch Oral Dent Res 2015; 2(1): 1-8.
24. M Maheshwari, G Miglani, A Mali, A Paradkar, S Yamamura and S Kadam: Development of tetracycline-serratiopeptidase-containing periodontal gel: formulation and preliminary clinical study. AAPS Pharm Sci Tech 2006; 7(3): 76.
25. NK Sharma and A Prasad: Evaluation of efficacy of tetracycline as a local drug delivery system in the treatment of chronic periodontitis as an adjunct to scaling and root planing – a clinical and microbiological study. International Journal of Con Medi Res 2017; 4(5): 998-03.
26. SA Abbas and G Ari: Minocycline ointment as a local drug delivery in the treatment of generalized chronic periodontitis - a clinical study. J Clin Diagn Res 2016; 10(6): 15-19.
27. Lorne M. Golub and Hsi Ming Lee: Periodontal therapeutics Current host-modulation agents and future directions. Periodontol 2020; 82(1): 186-04.
28. Polson AM, Garrett S, Stoller NH, Bandt CL, Hanes PJ and Killoy WJ: Multi-center comparative evaluation of subgingivally delivered sanguinarine and doxycycline in the treatment of Periodontitis. J Period 1997; 68: 119- 26.
29. Penmetsa GS, Subbareddy B, Mopidevi A, Arunbhupathi P, Baipalli V and Pitta S: Comparing the effecct of combination of 1% chlorhexiidne gluconate gel and Aloe Vera gel in the treatment of chronic periodontitis A rondomized single blind split mouth study. Contemp Clin Dent 2019; 10: 226-31.
30. Grover V, Kapoor A, Malhotra R, Battu VS, Bhatia A and Sachdeva S: To assess the effectiveness of a chlorhexidine chip in the treatment of chronic periodontitis: A clin and radiographic study. J Ind Soc of Period 2011; 15: 139-46.
31. Nanda Kumar PK: Local drug delivery-periocol in periodontics. Trends Biomater Artif Orga 2006; 19(2): 74-80.
32. Riep B, Purucker P and Bernimoulin JP: Repeated local metronidazole-therapy as adjunct to scaling and root planing in maintenance patients. J Clin Periodontol 1999; 26: 710-15.
33. Gautami S, Penmetsa, Bhavana P, Arunbhupati P, Meghana K, K ausalya P and Venkatalakshmi M: Comparative evaluation of the clinical efficacy of 3% satranidazole and 1% ornidazole gel through local drug delivery system in the treatment of chronic periodontitis. Research J Pharm and Tech 2020; 13(8): 3675-80.
34. Sugiarta AP, Lessang R and Natalina: Effect of herbal toothpaste containing neem leaves extract (azadirachta indica) against gingivitis: a clinical study. International Journal of Applied Pharmaceutics 2019; 11(1): 117-19.
35. M Sanchez, E Gonzalez-Burgos, Ie Igleisas and M Pilar Gomez-Serranillos: pharmacological update properties of aloe vera and its major active constituents. Molecules 2020: 25(6): 1324.
36. Dr S Abrol, Dr S Chhina, Dr SA Arora, Dr J Chand and Dr N Gupta: Efficacy of 2% cymbopogon citratus (lemongrass) gel as an adjunct to scaling and root planing-a clinical study based on phytoscience. World Journal of Pharmaceutical Research 2019; (9)2; 1102-13.
37. Mageed MJ and Saliem SS: Antimicrobial effects of green tea extracts on *Porphyromonas gingivalis*. J Dent Med Sci 2015; 14(10): 33-39
38. Elgendy EA, Abdel-Moula Ali S and Zineldeen DH: Effect of local application of tea tree (*Melaleuca alternifolia*) oil gel on long pentraxin level used as an adjunctive treatment of chronic periodontitis: A randomized controlled clinical study. J Ind Soc Periodontol 2013; 17(4): 444-48.
39. AM Sha and BT Garib: Biom Med Resear Inter 2019; 14.
40. Yaghini J, Shahabooei M, Aslani A, Zadeh MR, Kiani S and Naghsh N: Efficacy of a local drug delivery gel containing extracts of Quercusbrantii and *Coriandrumsa tivum* as an adjunct to scaling and root planing in moderate chronic periodontitis patients. J Res Pharma Pract 2014; 3(2): 67-71.
41. Hossam Abdelatty Eid Abdelmagyda, Dr Shishir Ram Shetty, Dr Manea Musa Musleh Al-Ahmarid. Herbal medicine as adjunct in periodontal therapies- A review of clinical trials in past decade. Journal of Oral Biology and Craniofacial Research 2019; 9(3): 212-17.
42. Rameshwari S, Vivek A, Pavitra R, Richa K and Shuchi T: Efficacy of *Acacia arabica* gum as an adjunct to scaling and root planing in the treatment of chronic periodontitis A randomized controlled clinical trial. Saudi Dental J 2018; 30(1): 53-62.
43. Gomes LA, Figueiredo LM, Palma AL, Geraldo BM and Castro KC: *Punicagranatum* L. (Pomegranate) Extract: *In-vivo* study of antimicrobial activity against porphyromona gingivalis in galleria mellonella model. Scientific World J 2016; 1-5.

How to cite this article:
Anarth R, Kale P, Mani A and Kendre S: Local drug delivery in periodontitis: an innovative treatment modality. Int J Pharm Sci & Res 2021; 12(9): 4616-25. doi: 10.13040/IJPSR.0975-8232.12(9).4616-25.