Local drug delivery systems in the treatment of periodontitis

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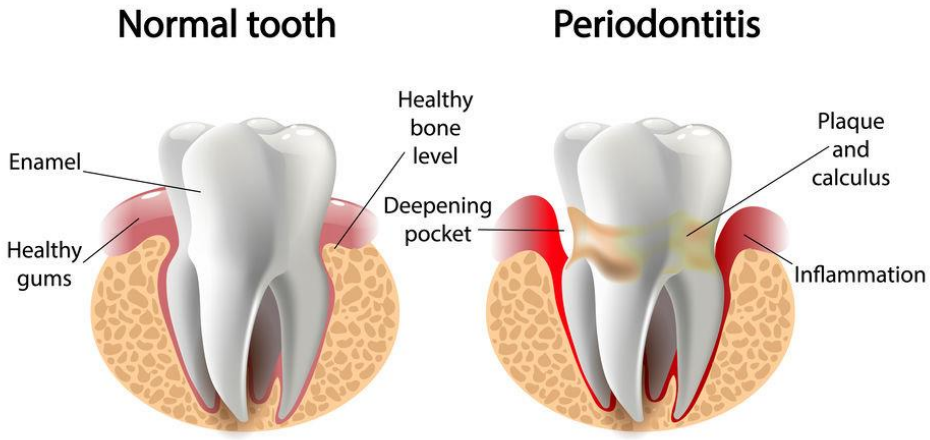
Periodontitis is a common disease of the oral cavity consisting of inflammation of the tooth supporting tissues, primarily caused by accumulation of complex polymicrobial dental plaque.

- It is one of the world's most prevalent chronic diseases

Primary causes of periodontitis are poor oral hygiene, alcohol, stress, tobacco, diet, immune disorders, and systemic diseases.

✓ The incidence of periodontal disease is closed related to bacterial infection

Anaerobic and gram negative microorganisms are the main bacteria related to periodontal disease



- Chronic periodontitis
- Aggressive periodontitis ⇒ Depressive mood, weight loss, loss of appetite, and fatigue

Healthy gingiva

Pellicle (Adsorption of salivary polypeptide and glycol proteins)

Plaque (Bacterial adhesion and aggregation)

Calculus/Tartar (Calcification of plaque)

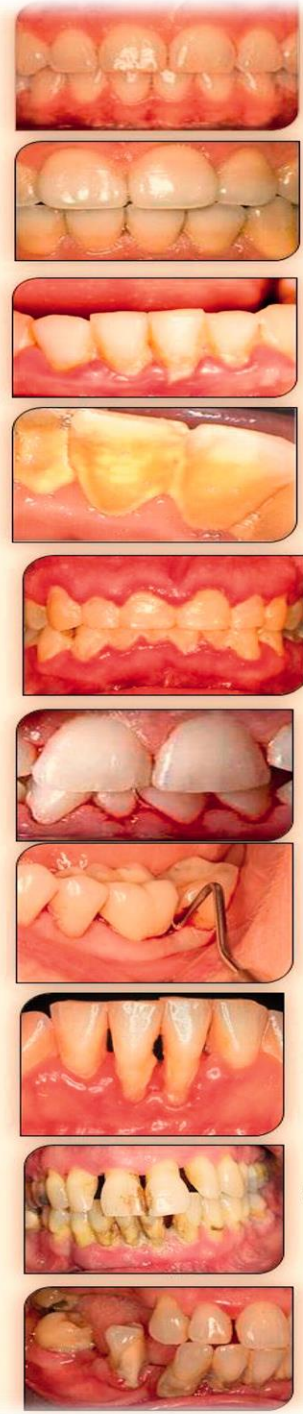
Gingivitis (Production of bacterial enzymes and toxins, inflammation)

Pyorrhea (Release of inflammatory mediators, inflammation, bleeding, bad breath)

Periodontal pocket (Degeneration of periodontal ligament and alveolar bone resorption)

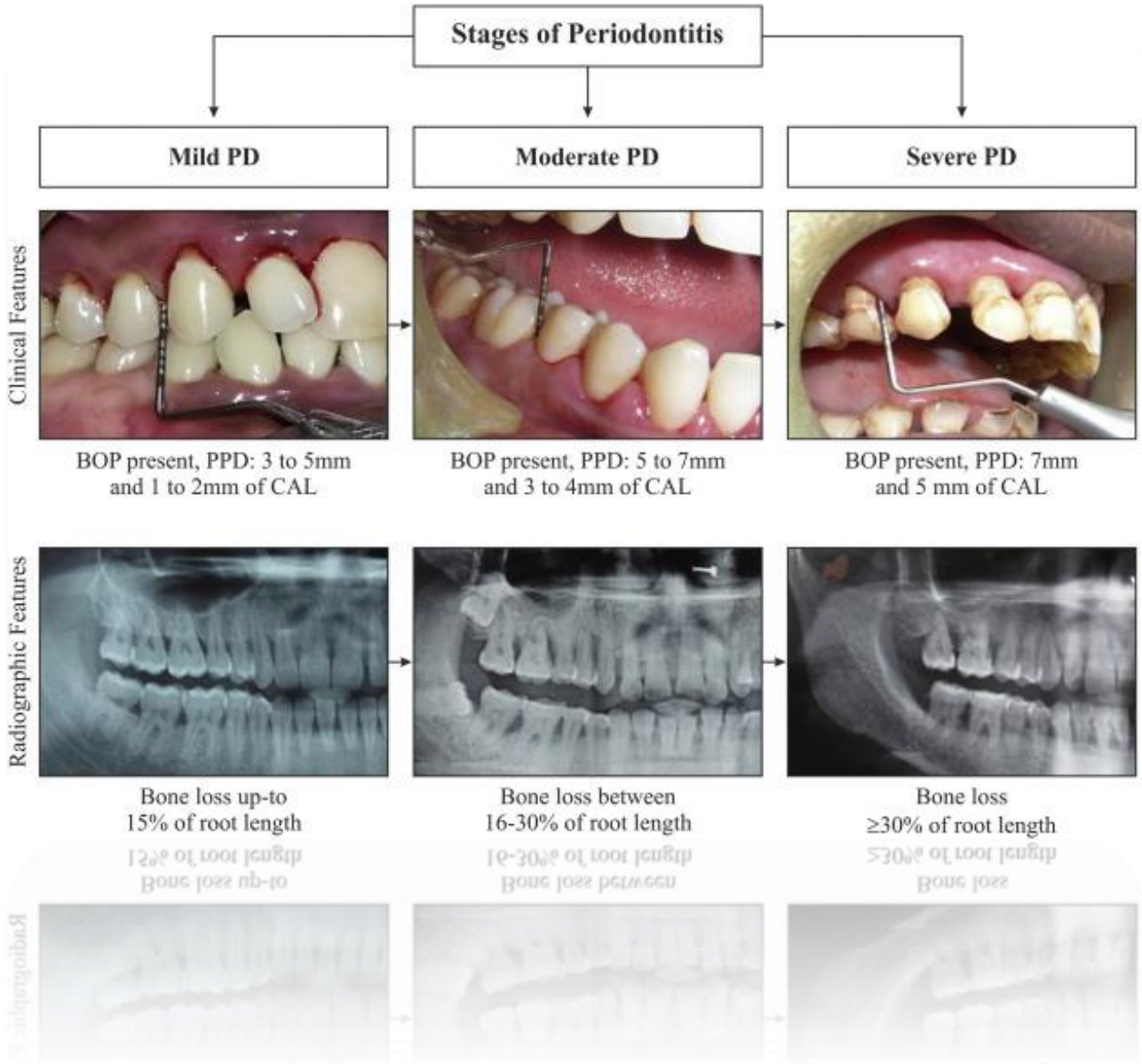
Periodontitis (Progression in periodontal tissue destruction , deepening of pockets and loosening of teeth)

Teeth loss

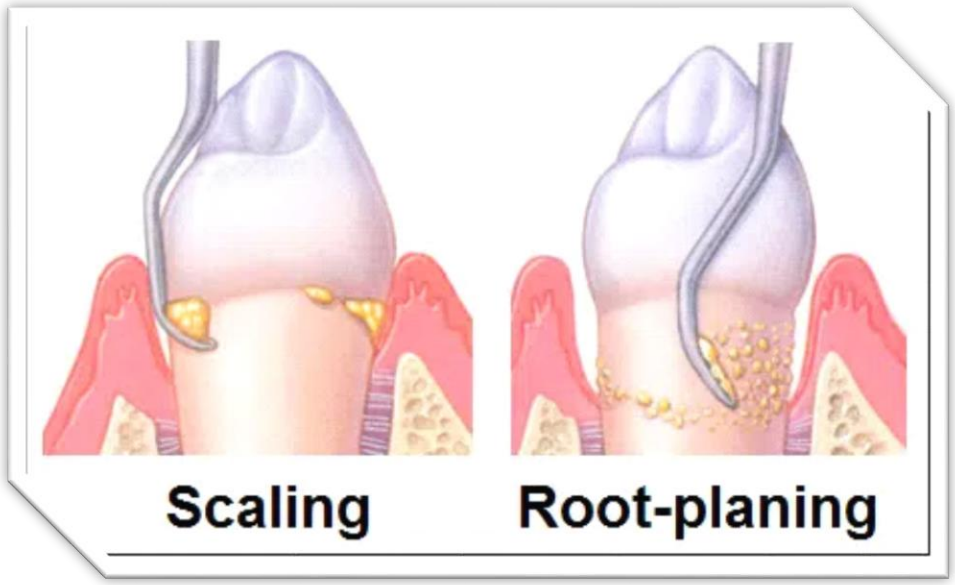


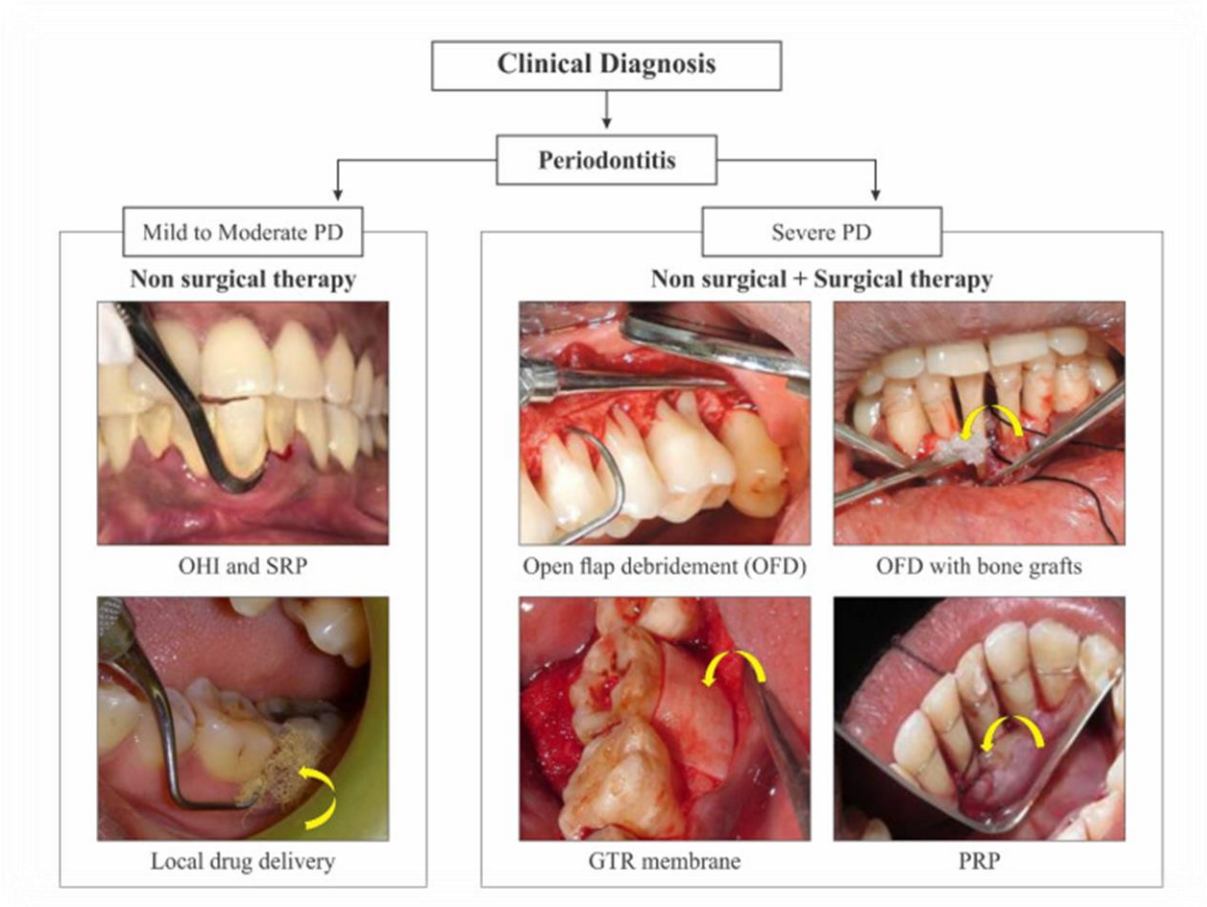
Moderate

Severe

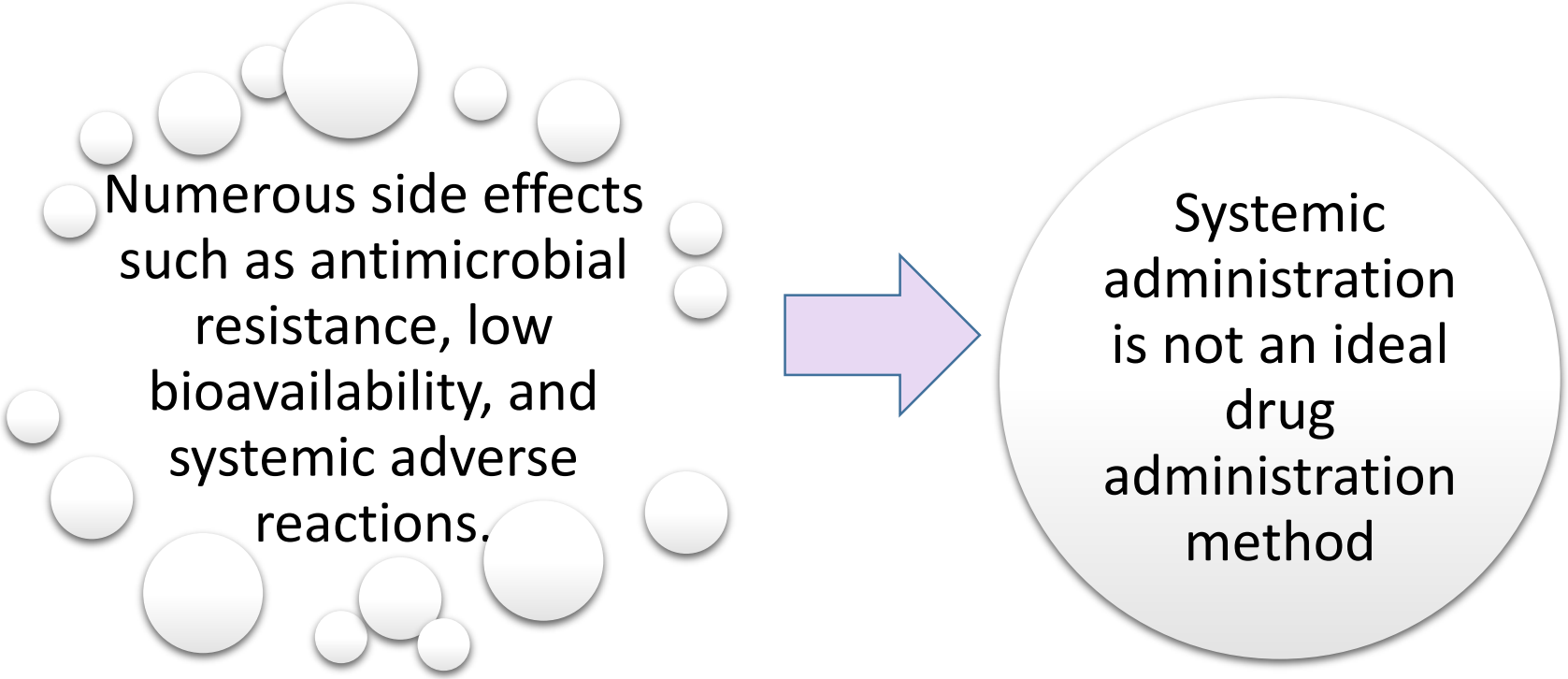

Stages of Periodontitis
Mild PD
Moderate PD
Severe PD
Clinical Features
BOP present, PPD: 3 to 5mm
and 1 to 2mm of CAL
BOP present, PPD: 5 to 7mm
and 3 to 4mm of CAL
BOP present, PPD: 7mm
and 5 mm of CAL
Radiographic Features
Bone loss up-to
15% of root length
Bone loss between
16-30% of root length
Bone loss
≥30% of root length

- The most basic way to treat periodontal disease is to use periodontal scaling and root planning to remove plaque and calculi on the surface of teeth.





- Because periodontal disease is an inflammatory disease closely related to bacterial infection, to improve the curative effect, periodontal disease management often cooperates with the use of anti-microbial agents and anti-inflammatory drugs.



- Nowadays, local drug delivery has become a common way of drug administration for periodontal tissue

> The key to success for periodontal therapy depends on the selection of an appropriate antimicrobial agent with appropriate route of drug administration

- Various studies have revealed that LDD into the periodontal pockets can provide higher therapeutic concentrations of the antibiotic compared to the systemic administration

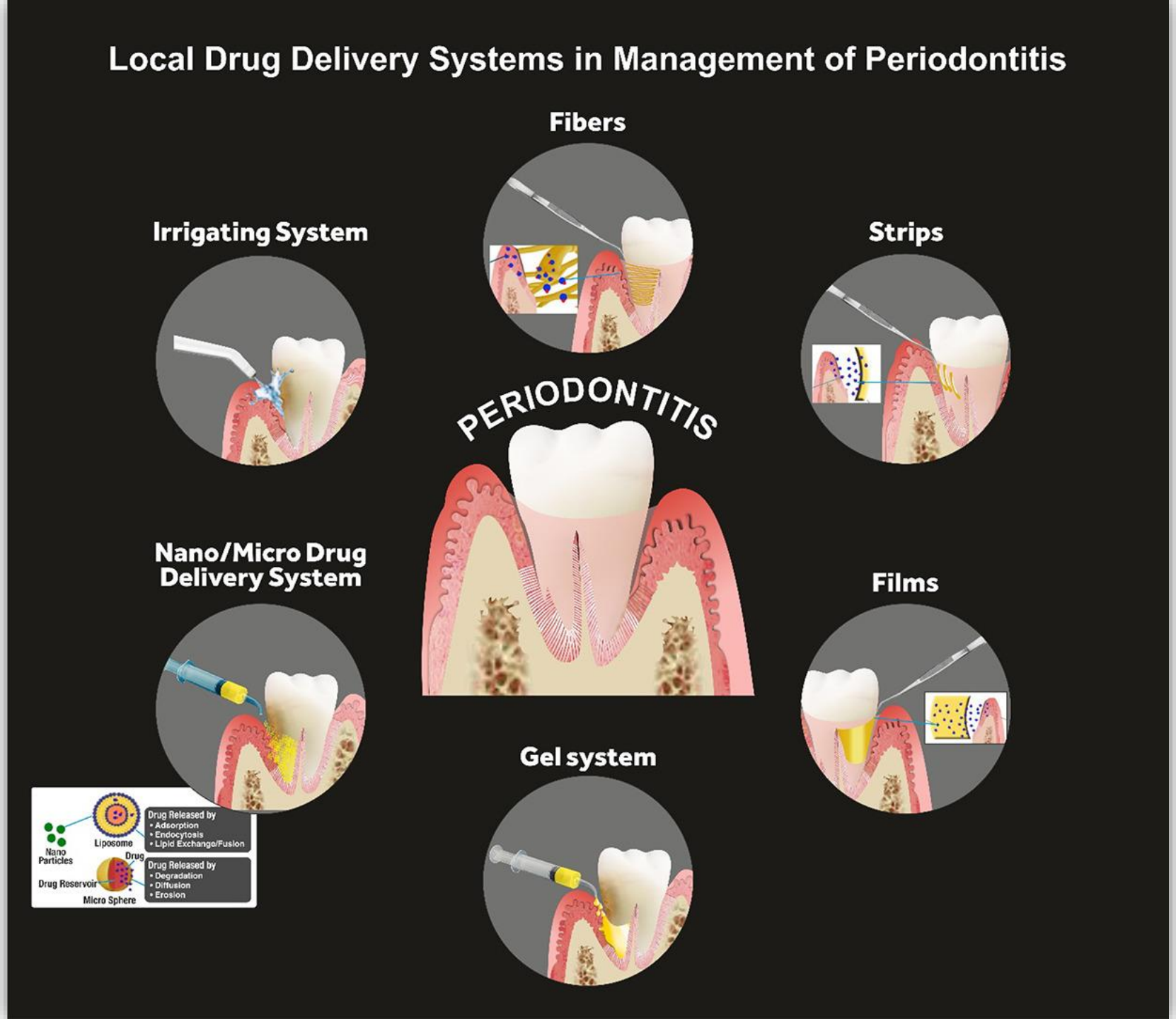
Advantages of local drug delivery into periodontal pocket are as follows:

- ✓ Direct access to target diseases
- ✓ Improvement of patient compliance
- ✓ Bypass of first-pass metabolism by the liver
- ✓ Enhanced therapeutic efficacy of the drug
- ✓ Reduced treatment cost
- ✓ Reliable drug delivery route in very sick patients who are unable to swallow
- ✓ Safer and more convenient route of drug administration
- ✓ Longer duration of action can be achieved
- ✓ Noninvasive, painless and simple application

- The most important requirements for a drug delivery device in periodontitis treatments are the delivery of antimicrobial agents in those areas where mechanical scaling instruments cannot access and the release of the level of active agent required throughout the entire treatment period

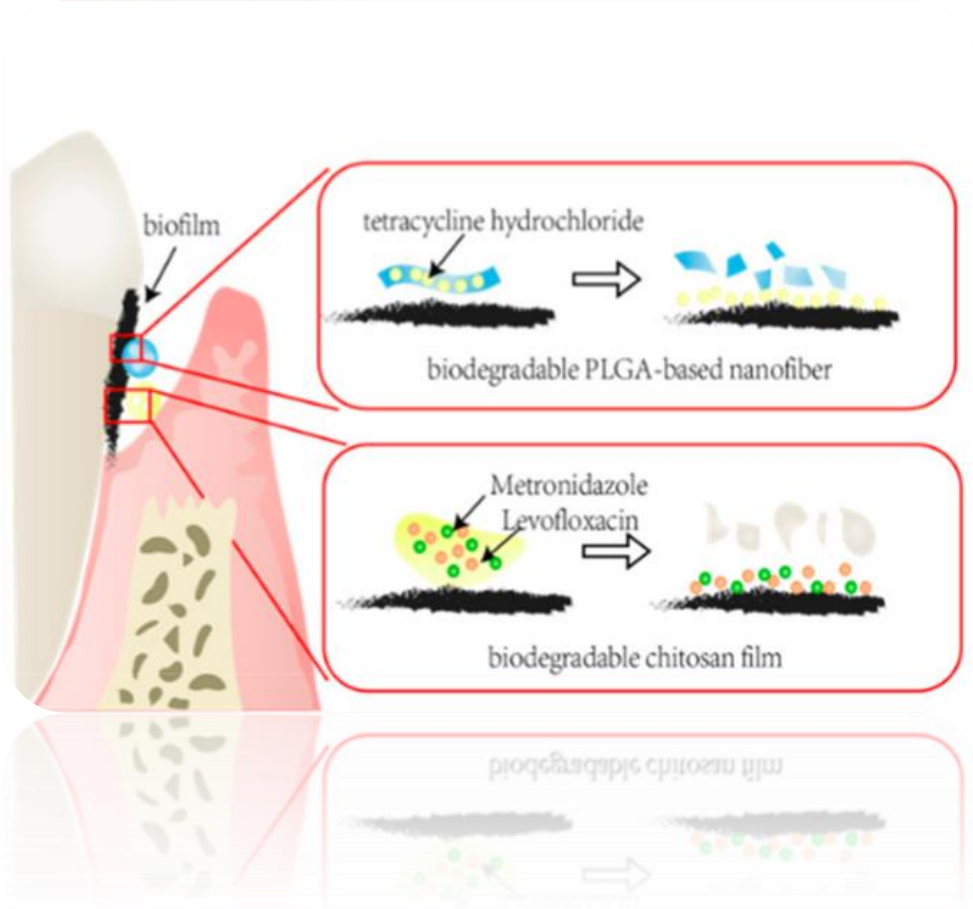
The rate of drug release from novel controlled drug delivery devices can be precisely controlled. By the use of a variety of polymers, these formulations have proved to be superior due to low price, higher stability, nontoxicity, biocompatibility, nonimmunogenicity and biodegradability

Local Drug Delivery Systems in Management of Periodontitis



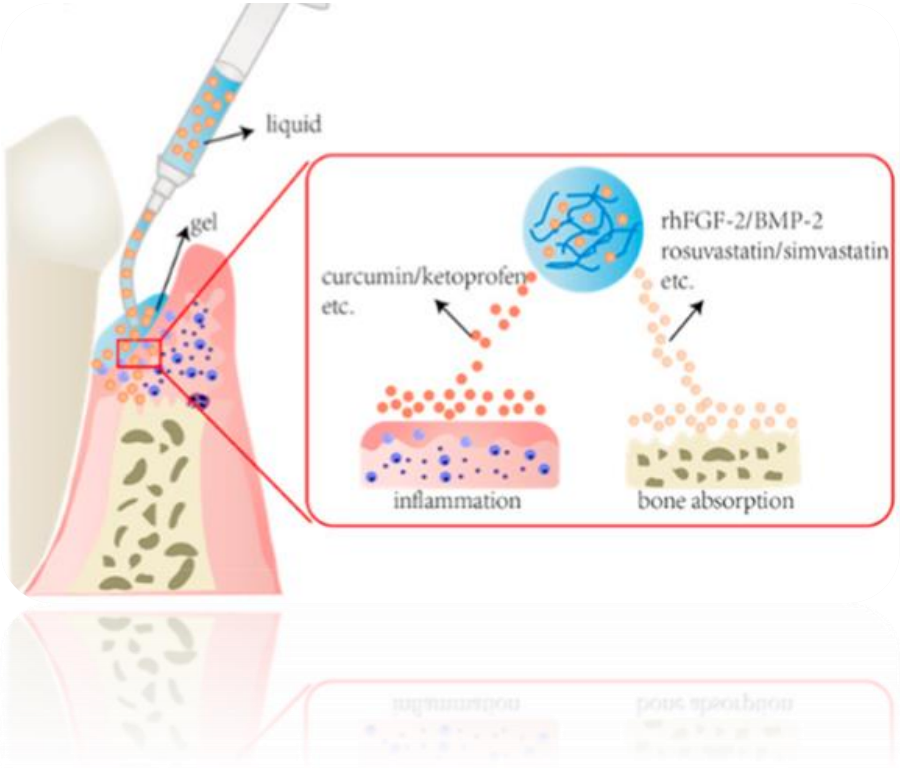
✓ Anti-Bacterial DDS for Periodontitis

tetracycline (TET), doxycycline (DOX), minocycline (MIN), metronidazole (MTZ), chlorhexidine (CHX), clarithromycin (CLM), azithromycin (AZM), moxifloxacin (MXF), clindamycin (CLI), and satranidazole (SZ)



✓ Inflammation Modulating and Alveolar Bone Repairing DDS for Periodontitis

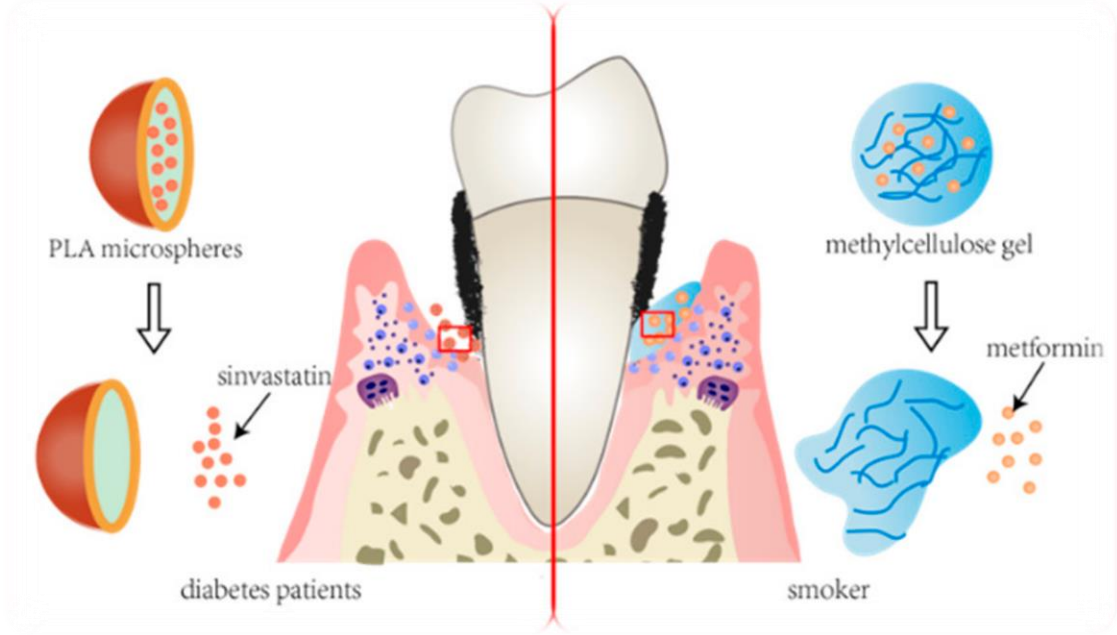
- Periodontitis is a process of the inflammatory response and can lead to the absorption of alveolar bone. So, to control periodontitis, there are also drug delivery systems for immunomodulation and alveolar bone repair, which usually load drugs that have anti-inflammatory effects or promote bone repair



- Treatments of Periodontitis Associated with Systemic Diseases

diabetes

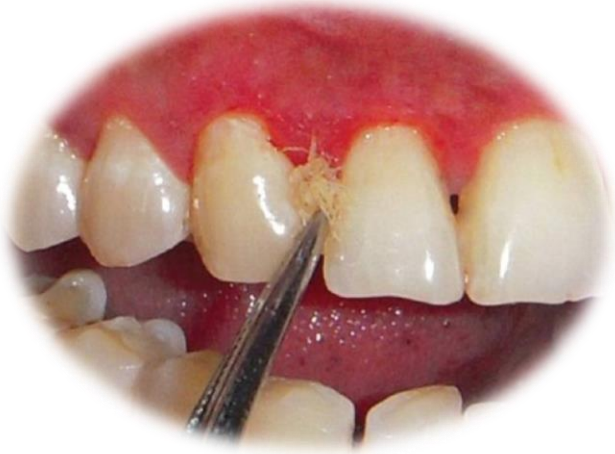
Smoking



Fibers

Fibers are reservoir type of therapeutic formulation system that are placed circumferentially into the periodontal pocket using an applicator and sealed with a cyanoacrylate adhesive or a periodontal dressing

- ✓ Chitosan
- ✓ gelatin
- ✓ poly (lactide-co-glycolide) (PLGA)
- ✓ poly (caprolactone) (PCL)
- ✓ ethylene vinyl acetate (EVA)
- ✓ cellulose acetate



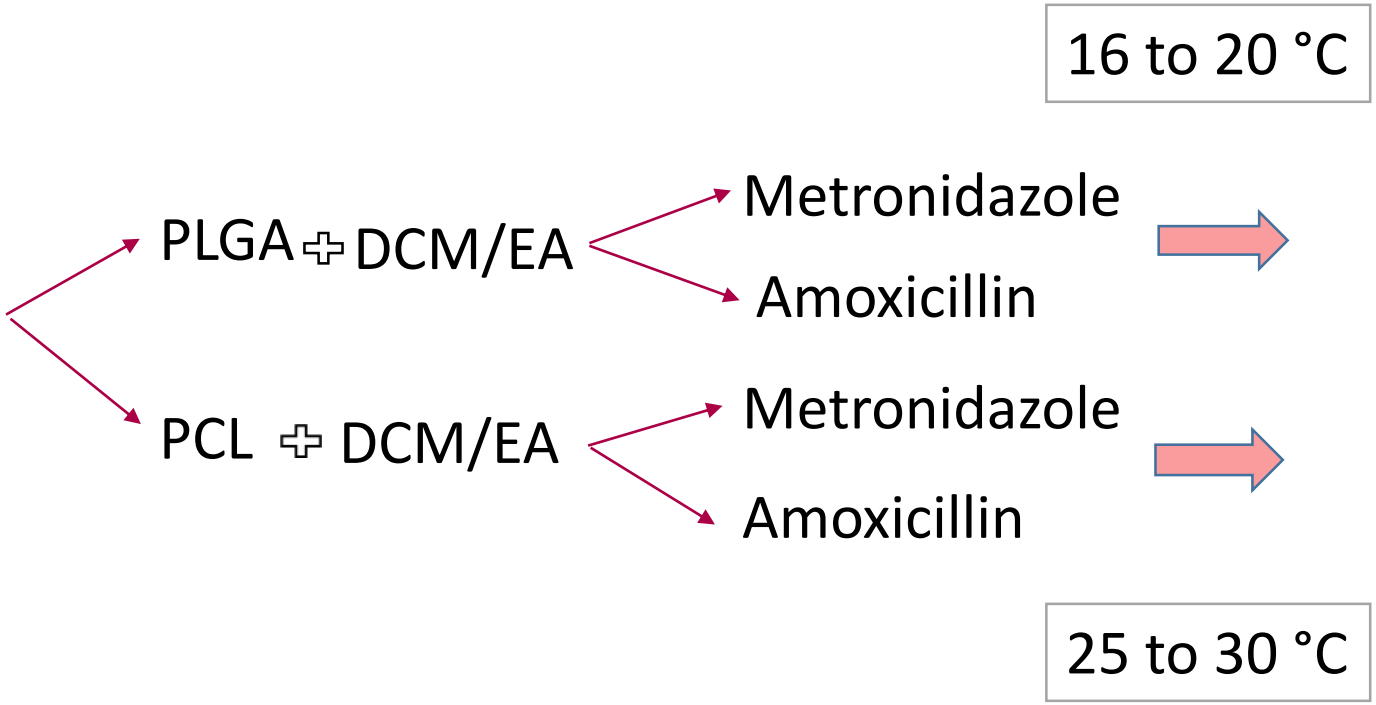
Metronidazole- and Amoxicillin-Loaded PLGA and PCL Nanofibers as Potential Drug Delivery Systems for the Treatment of Periodontitis: In Vitro and In Vivo Evaluations

- ✓ Antibiotic therapy is necessary for the eradication of microbial plaque because of its important role in the progression of periodontitis.

- ✓ One of the common methods is the use of combination therapy (combination of amoxicillin with metronidazole). This is especially effective against aggressive types of periodontitis.

- PLGA
- PCL

good mechanical properties
high biocompatibility
nontoxicity in the body

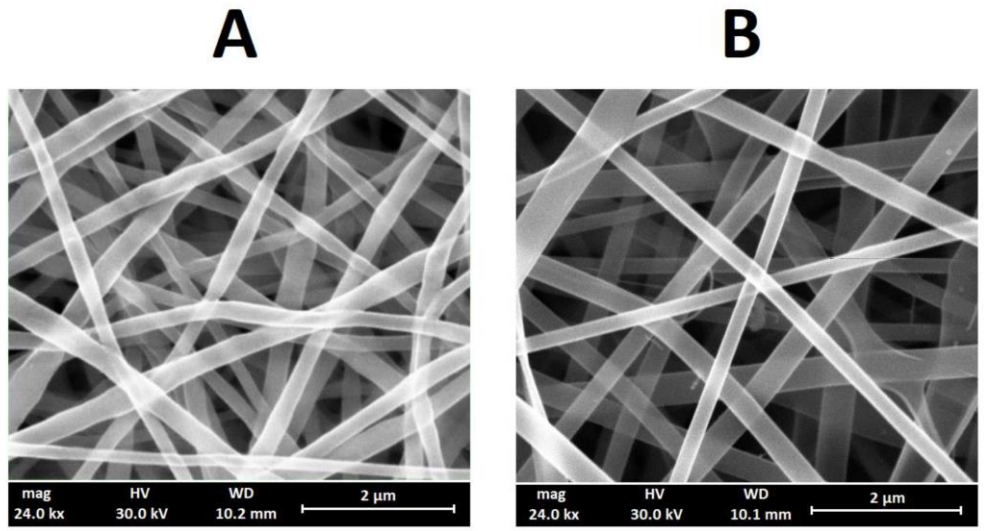


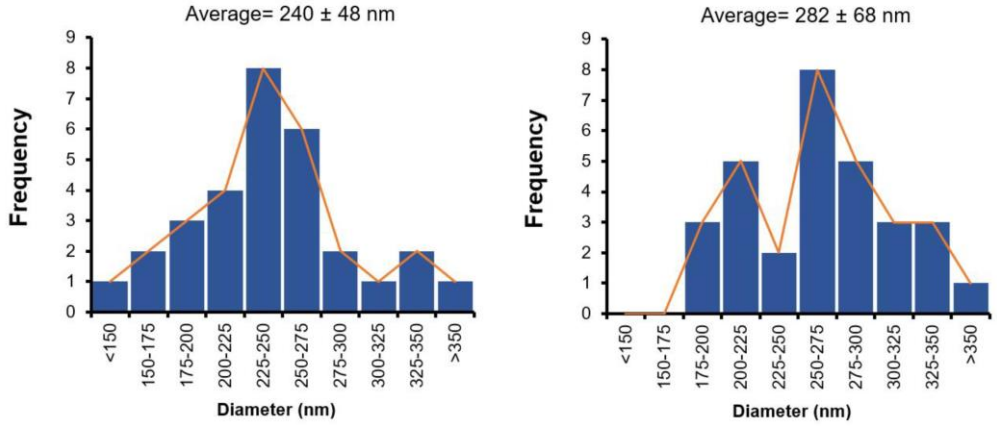
- ✓ maximum voltage of 17 kV
- ✓ drum rotation rate of 250 rpm
- ✓ The needle was swept between distances of 110 to 190 mm from the baseline
- ✓ distance of 100 mm between the needle and the drum

SEM

- surface morphology
- uniformity
- structure

The larger diameter obtained for the PCL fibers may have been due to the higher viscosity of the electrospinning solution arising from the higher molecular weight of PCL (Mw = 80,000) compared to PLGA (Mw = 20,000)





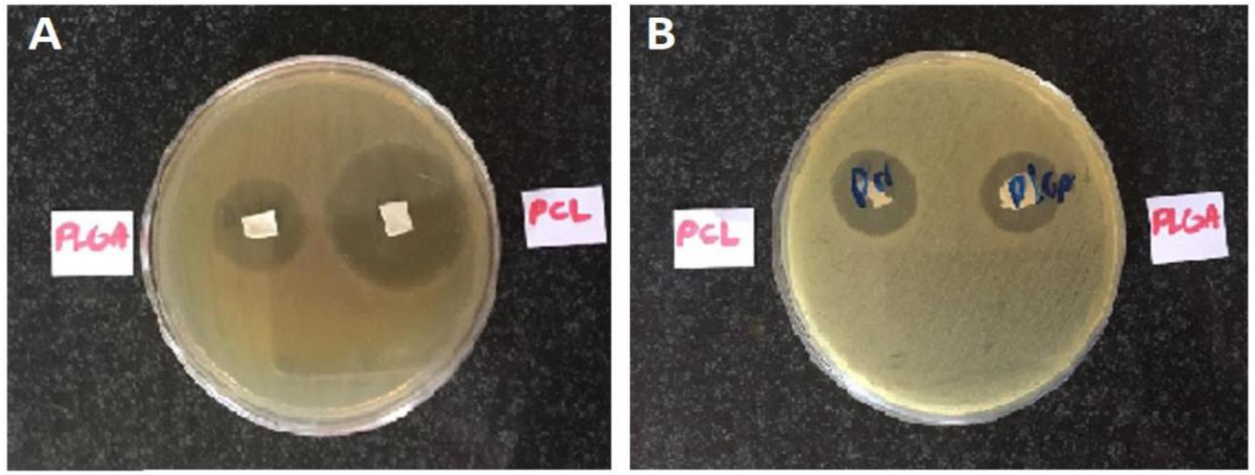
Tensile Strength Measurement

- ✓ the PLGA nanofibers were more resistant to tension than the PCL nanofibers when external stress was applied.
- ✓ Drug-loading can lead to decreased tensile stress.
- ✓ The tensile strength of nanofibers is highly related to the porosity and to the width-to-length ratio of the mat and each strain of fiber.

Sterility Test

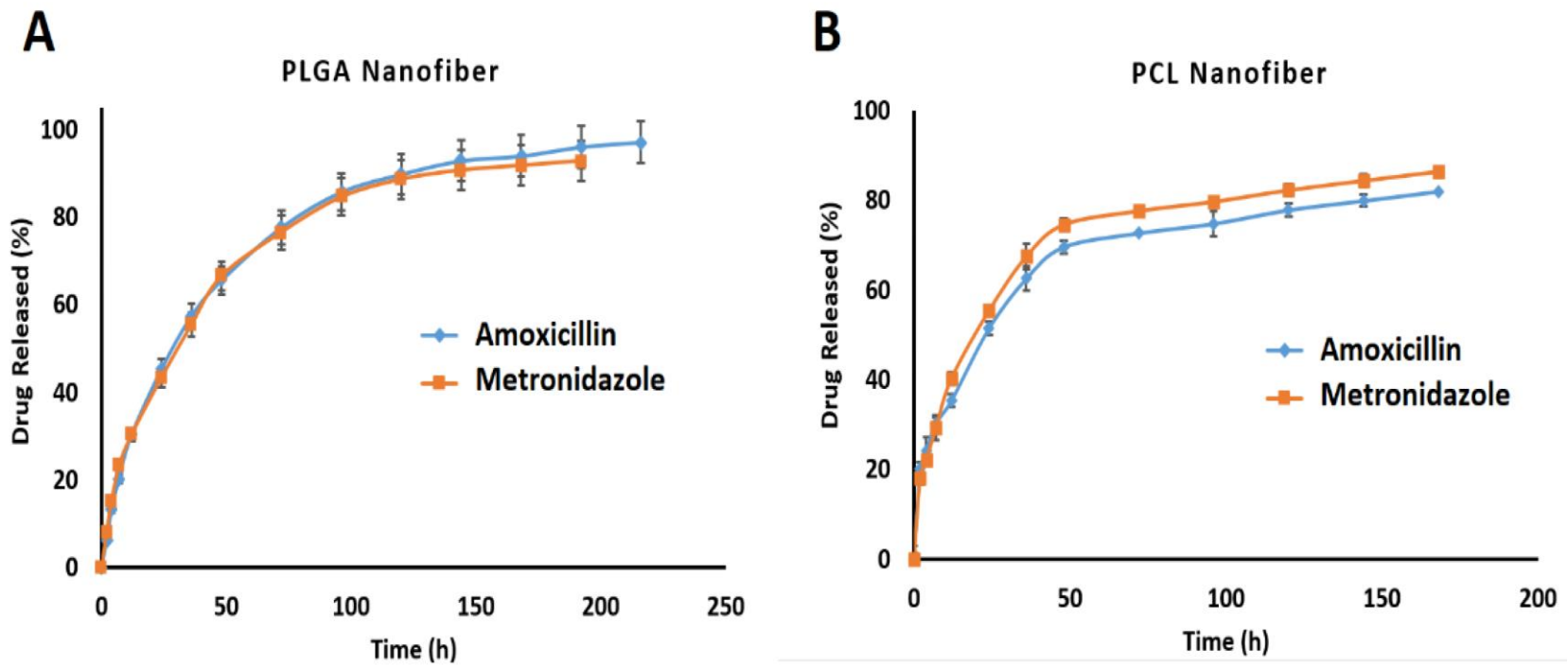
- ✓ No microorganism growth was detected in all the culture media, indicating the sterility of the prepared nanofibers.

Microbial Assay



The inhibition growth zones and antimicrobial efficacy of the prepared nanofibers against S. aureus (A) and E. coli (B)

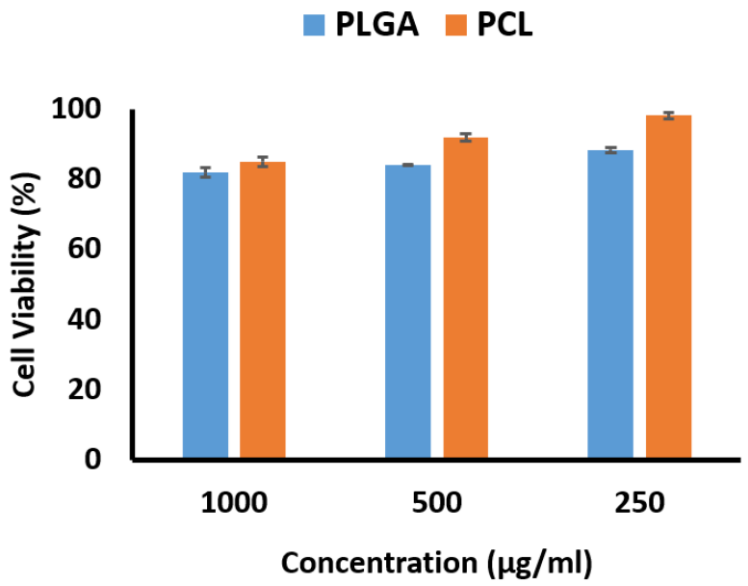
In Vitro Drug Release



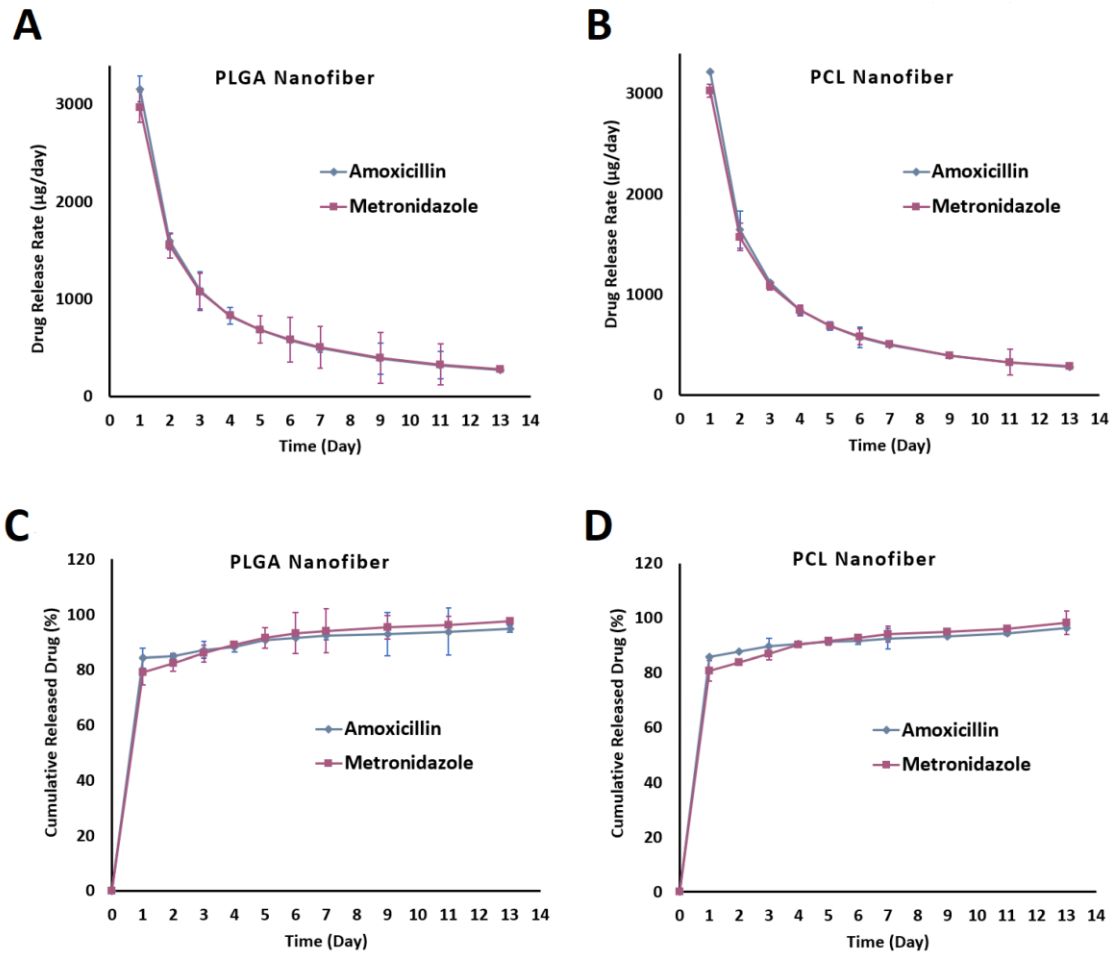
Drug Release Kinetics

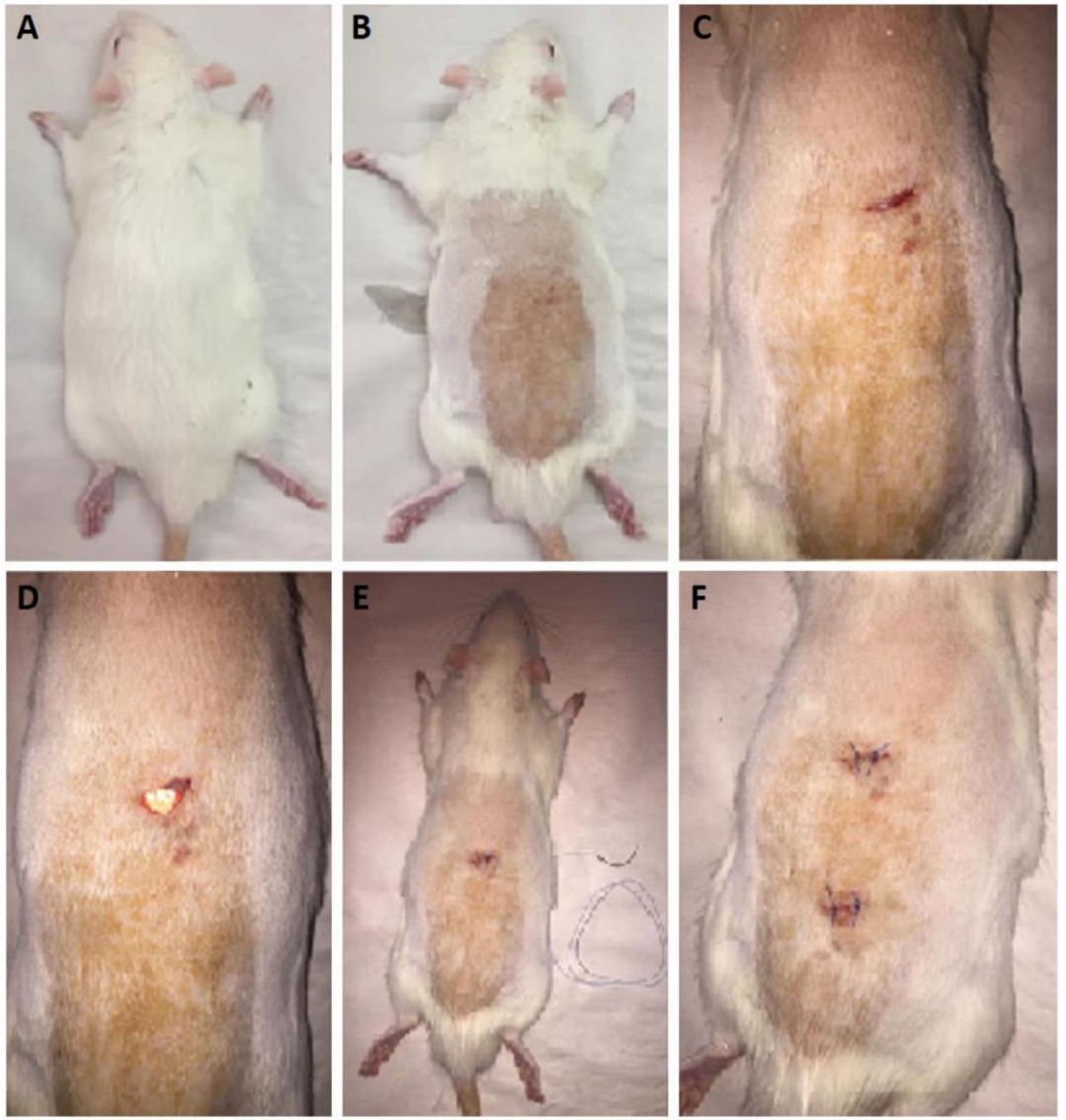
- ✓ The Higuchi model was the best-fitted model for the drug releases from the PLGA and PCL nanofiber formulations.

Cytotoxicity Evaluation



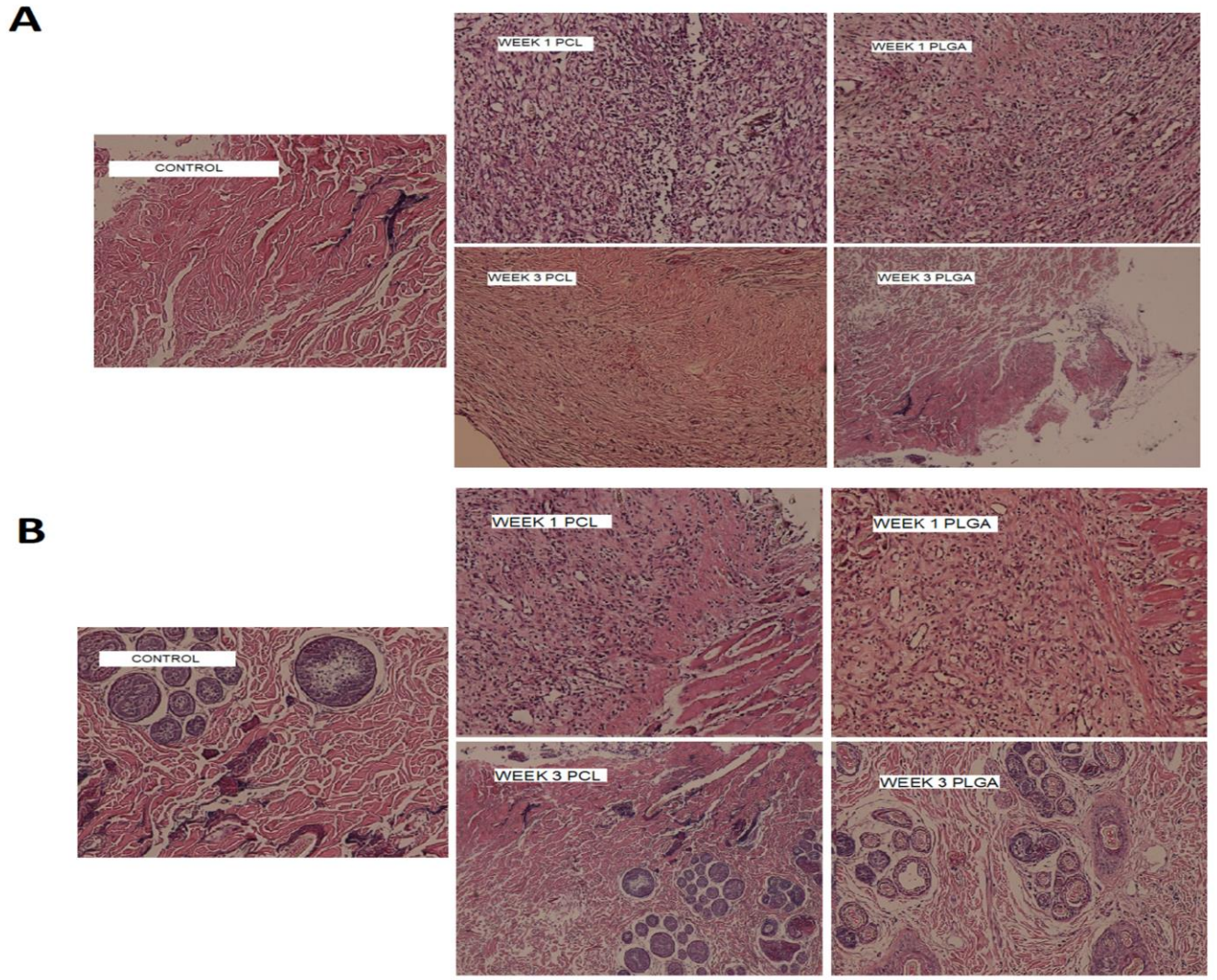
In Vivo Drug Release





In Vivo Biocompatibility

- ✓ The PLGA nanofibers were more biocompatible compared to the PCL nanofibers.



- Nanofibers are one of the most promising formulations for use in modified release systems for direct drug delivery that are made of polymers that are compatible with body tissues.

- Nanofibers were able to release their drug contents in a controlled manner and keep the concentration of the drug at the right level in the local area to treat the infection.

- The prolonged-release profiles indicate that these systems could increase patient compliance by reducing the administration frequency. It can therefore be concluded that these systems have the potential to enter clinical studies and to be used as routine effective treatment modalities against periodontitis.

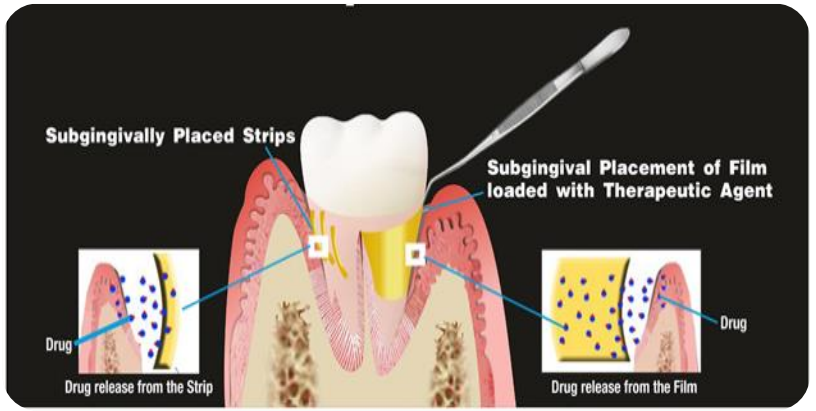
strips and films

Strips and films (SF) are polymer based thin bands of matrix system designed to deliver the active therapeutic agents in a controlled and sustained fashion when precisely placed in the interproximal periodontal pocket space

- ✓ polylactic acid
- ✓ polyglycolic acid
- ✓ poly-caprolactone
- ✓ poly hydroxyl butyric acid (PHBA)
- ✓ ethyl cellulose
- ✓ cellulose acetate
- ✓ ethyl methacrylate

- Release pattern and the biodegradable nature of SF system depends on the polymer and crosslinking agents used. In general, drug release from SF critically depends on their biodegradable property of the polymer which occurs either by diffusion of drug and/or matrix dissolution or erosion.

SF has the advantage of being easily manipulated for desired shape and size to match the pocket dimensions that allows for easy insertion with minimal discomfort to the patient.

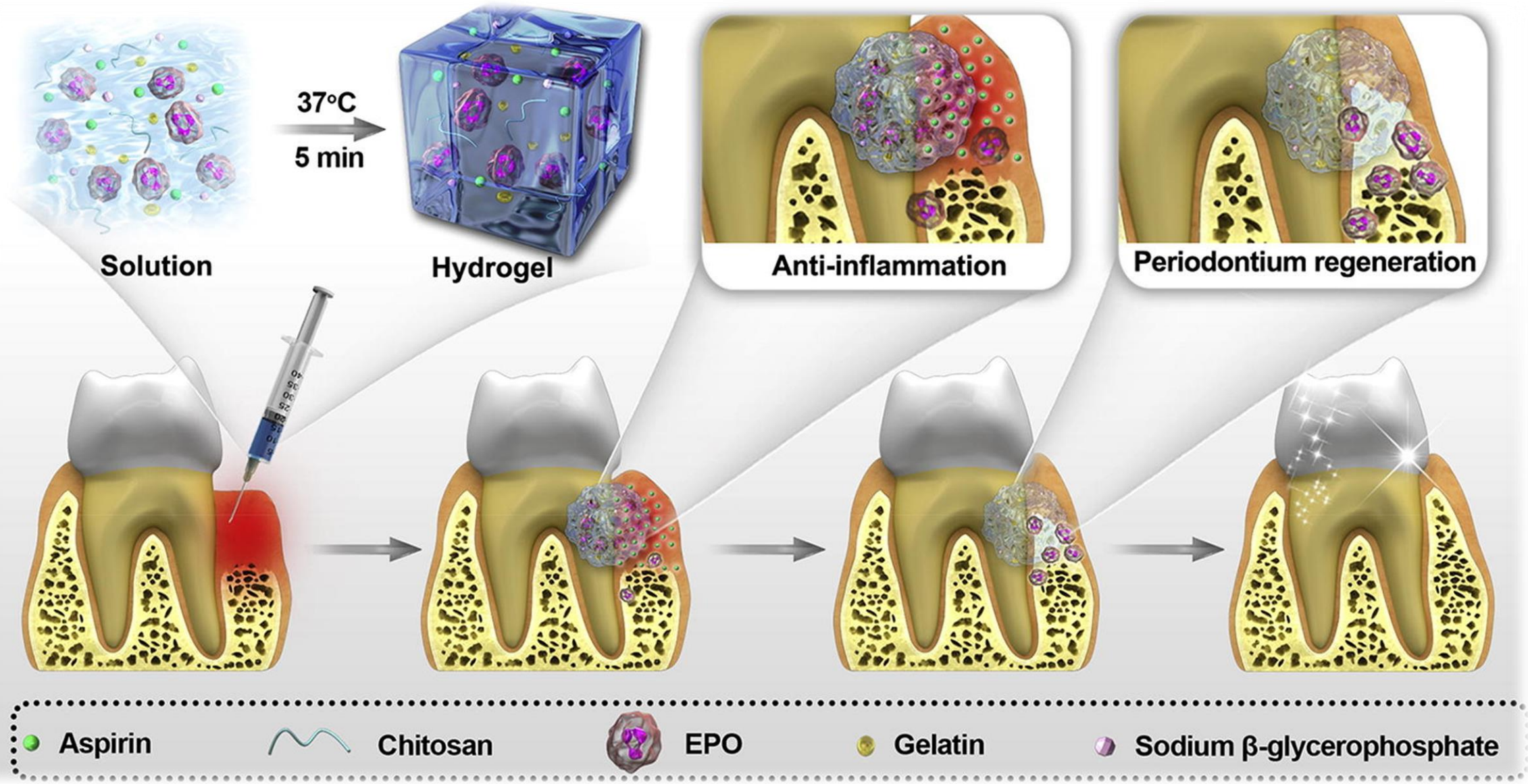


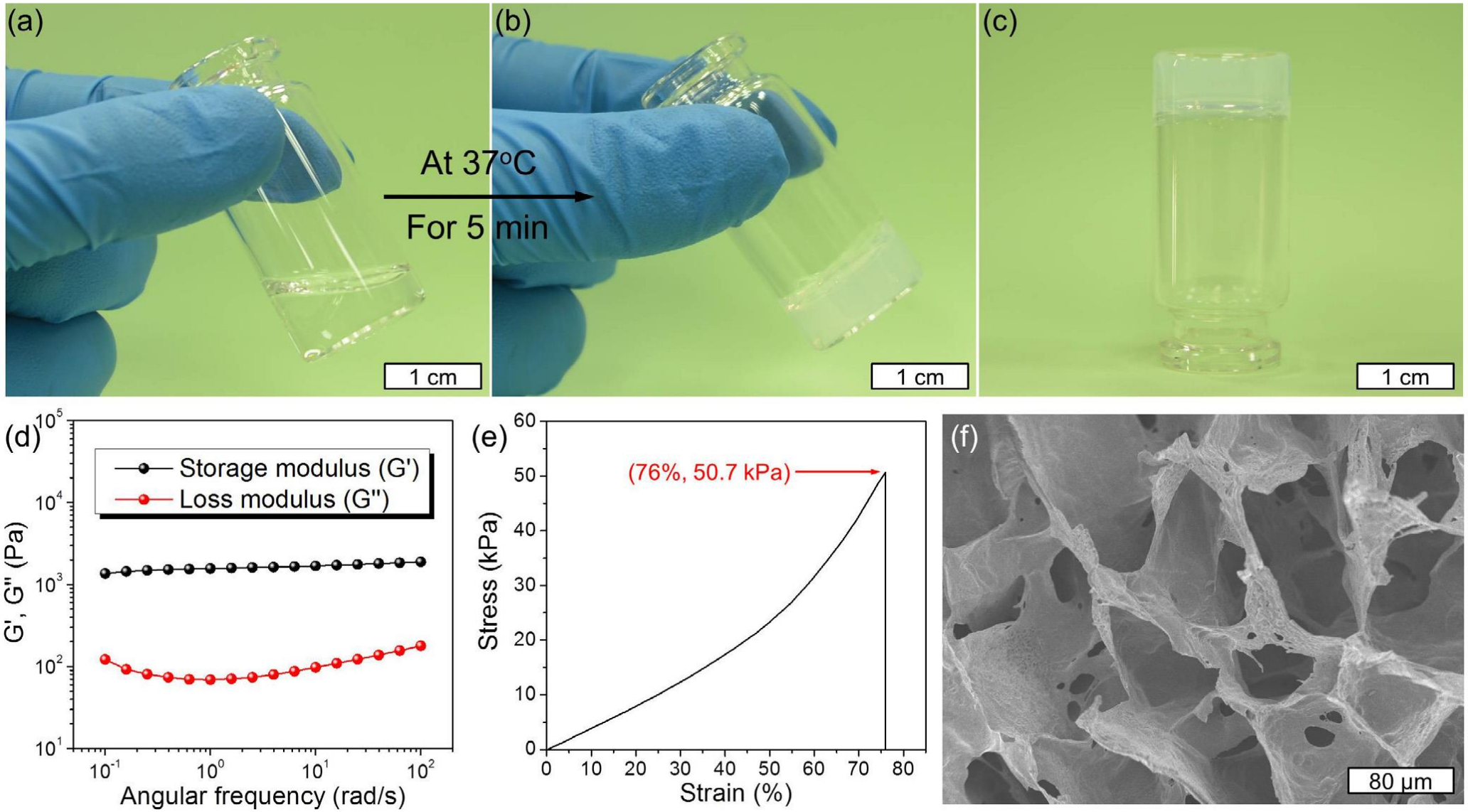
Gels

Gels get the maximum credit in the general dental practise for being used ubiquitously as a carrier system to deliver therapeutic agents in a wide range of oral diseases.

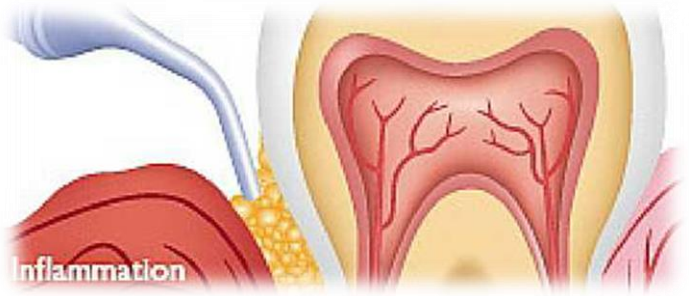
- Polymer science has progressed exponentially over the years and has resulted in the development of novel gel formulations that are transformed from liquid state to semisolid gel state depending on the type of stimulus such as pH change, magnetic field and temperature .

- ✓ Carbopol
- ✓ Xanthan
- ✓ Carboxy methyl cellulose
- ✓ Chitosan


37°C
5 min
Solution
Hydrogel
Anti-inflammation
Periodontium regeneration
Aspirin
Chitosan
EPO
Gelatin
Sodium β-glycerophosphate


(a)
(b)
(c)
At 37°C
For 5 min
1 cm
1 cm
1 cm
(d)
Storage modulus (G')
Loss modulus (G")
G', G" (Pa)
Angular frequency (rad/s)
(e)
(76%, 50.7 kPa)
Stress (kPa)
Strain (%)
(f)
80 μm

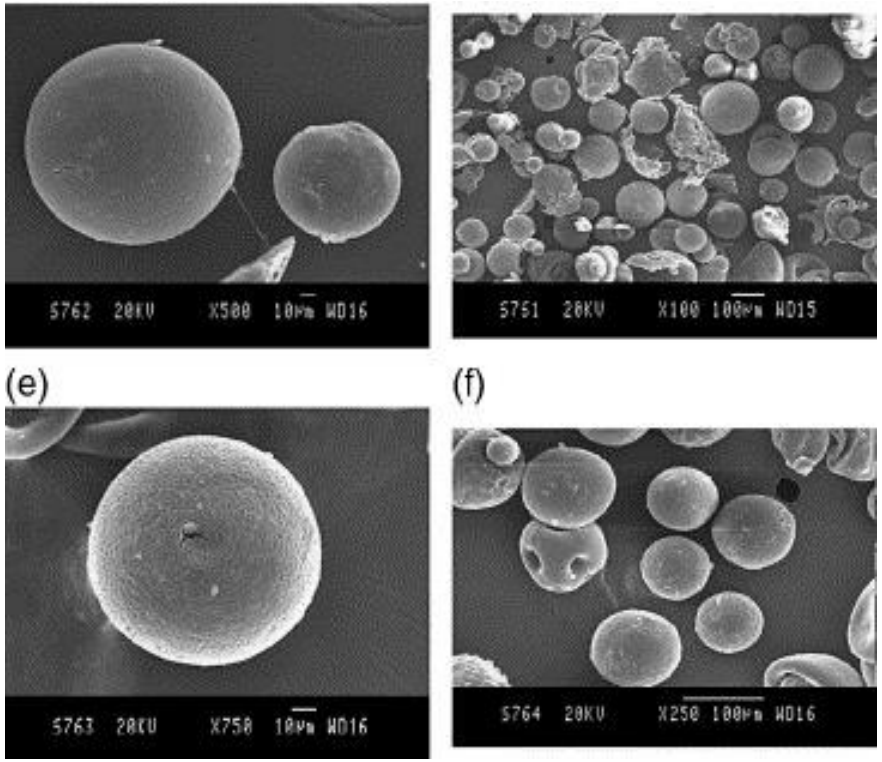
Microparticulate system



- allows protection of drugs from the external environment
- elimination of incompatibility
- masking of unpleasant taste
- enhance bioavailability
- sustained therapeutic activity

- Microparticles can be delivered via various carrier systems like chips, dental pastes/ gel systems and direct injection into the pocket.

- ✓ polyesters
- ✓ polyanhydrides
- ✓ natural polymers like chitosan
- ✓ hyaluronic acid
- ✓ alginic acid
- ✓ gelatin
- ✓ ethyl cellulose
- ✓ Polymethacrylates
- ✓ cellulose esters
- ✓ polyvinyl derivatives



Nanoparticulate drug delivery system

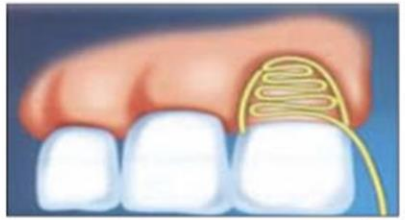
Silver, gold, titanium dioxide and copper NP are some of the most widely researched metallic nanoparticles in dentistry and other biomedical field due to their antimicrobial, anticancer, and bone regeneration potential.

- In periodontics, metallic and polymeric NP, nanofibers, liposomes, quantum dots, and nanocomposites/nanogels have been studied in various in-vitro and clinical studies.

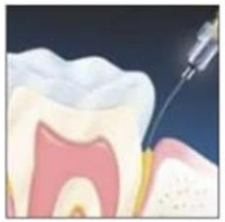
Systems	Advantages	Limitation
Fibers	Can be used in pockets in inaccessible areas, such as the last tooth in the dentition	Need to be removed after treatment; lead to various degrees of gingival redness
Strips and films	Thin and flexible; easy to insert with minimal discomfort to the patient	Rapid release in most cases; drug deliver to a small area of mucosa, thereby limiting the delivered dose
Microparticles	Ease of administration; Prolonged drug release	Not readily retained at the targeted site
Nanosystems	Able to be precisely applied to the target site, for example, the periodontal pocket areas below the gum line	Not readily retained at the targeted site; complex production process; lack of stability
Gel	Ease of administration; good patient acceptability; can keep in place and prolong the action time	Relatively large dosing volumes

List of commercial periodontal products presented in various dosage formS

Product	Antimicrobial Agents	Dosage Form	Manufacturer
Actinide®	Tetracycline	Non resorbale fiber	Alzacorp
Arestin®	Minocycline	Biodegradable powder in syringe	Oropharma corp Warminster
Atridox®	Doxycycline	Biodegradable mix in syringe	Atrix Labs,Ft,Collins, Co
Dentamycin®	Minocycline	Biodegradable mix in syringe	Sunstar Corp., Tokyo, Japan
Elyzol®	Metronidazole	Biodegradable mix in syringe	Dumex Corp.Co Denmark
Periochip®	Chlorhexidene	Biodegradable device	Dexcel Pharma Inc Jerusalem
Periochop®	Chlorhexidene /Tetracycline	Film	Perioproducts Ltd.
Periochip®	Gluconate	Inserts	Perioproducts Ltd.
Gluconate®	Metronidazole	Inserts	Perioproducts Ltd.
Elyzol®	Minocycline	Gel	Dumex pharma
Atrigel®	Doxycycline	Gel	Atridox (atridox lab)

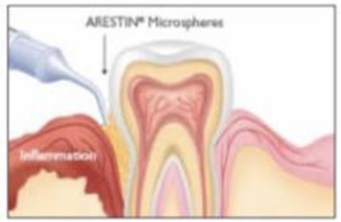


25%w/v tetracycline HCl

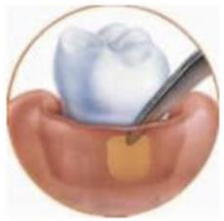


10% Doxycycline

25% Metronidazole



2% Minocycline



2.5mg Chlorhexidine

Conclusions and future perspectives

- ✓ With the increment in understanding of periodontal disease and the drug administration methods, various targeted delivery systems have been designed contributing in eradication of the systemic side effects of antibiotics.

- ✓ A shift from nonbiodegradable polymers to a variety of biodegradable polymers has helped in achieving biocompatible sustained release formulations, reduced the dosage frequency and thus minimized the chances of bacterial resistance.

- ✓ In order to achieve enhanced therapeutic effects, LDDS should be adequately exploited to release beneficial agents such as growth factors, osteogenesis drugs, human periodontal ligament stem cells, and adhesion factors at the wound site.

- ✓ The release sequence and release rate of drugs could be effectively controlled by a dual or even multiple LDDS.
- ✓ Importantly, this kind of LDDS will have all-inclusive therapeutic effects because it can deliver multiple drugs depending on the need of treatment at the same time.
- ✓ The nanoparticles-in-gel delivery system with time-programmed drug release could be applied to the treatment of periodontitis.
- ✓ In future, it might be possible to guide regeneration of tooth-supporting tissue, stimulate new bone formation and re-osseointegration by inducing specific cellular responses in the site cells.
- ✓ Gene-based therapeutics may play a significant role in the refractory periodontitis treatment in the coming years.

References

1- Liang J, Peng X, Zhou X, Zou J, Cheng L. Emerging applications of drug delivery systems in oral infectious diseases prevention and treatment. Molecules. 2020;25(3):516.

2- Wei Y, Deng Y, Ma S, Ran M, Jia Y, Meng J, et al. Local drug delivery systems as therapeutic strategies against periodontitis: a systematic review. J Control Release. 2021;333:269–82.

3- Sholapurkar A, Sharma D, Glass B, Miller C, Nimmo A, Jennings E. Professionally delivered local antimicrobials in the treatment of patients with periodontitis—A narrative review. Dent J. 2020;9(1):2.

4- Rajeshwari HR, Dhamecha D, Jagwani S, Rao M, Jadhav K, Shaikh S, et al. Local drug delivery systems in the management of periodontitis: A scientific review. J Control Release. 2019;307:393–409.

5- Joshi D, Garg T, Goyal AK, Rath G. Advanced drug delivery approaches against periodontitis. Drug Deliv. 2016;23(2):363–77.

6- Mirzaeei S, Mansurian M, Asare-Addo K, Nokhodchi A. Metronidazole-and amoxicillin-loaded PLGA and PCL nanofibers as potential drug delivery systems for the treatment of periodontitis: in vitro and in vivo evaluations. Biomedicines. 2021;9(8):975.

7- Xu X, Gu Z, Chen X, Shi C, Liu C, Liu M, et al. An injectable and thermosensitive hydrogel: Promoting periodontal regeneration by controlled-release of aspirin and erythropoietin. Acta Biomater. 2019;86:235–46.

8- Ramesh A, Prakash AP, Thomas B. Local Drug Delivery in periodontal diseases……. A Review. J Heal Allied Sci NU. 2016;6(01):74–9.

9- Khan G, Yadav SK, Patel RR, Nath G, Bansal M, Mishra B. Development and evaluation of biodegradable chitosan films of metronidazole and levofloxacin for the management of periodontitis. Aaps Pharmscitech. 2016;17(6):1312–25.

10- Ranjbar-Mohammadi M, Zamani M, Prabhakaran MP, Bahrami SH, Ramakrishna S. Electrospinning of PLGA/gum tragacanth nanofibers containing tetracycline hydrochloride for periodontal regeneration. Mater Sci Eng C. 2016;58:521–31.

Thanks for your attention