LOCAL DRUG DELIVERY

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INTRODUCTION

•Periodontal diseases are chronic inflammatory disease in which microbial factors, host factors, environmental and genetic factors play a significant role in causing the disease.

• In that dental plaque is considered as the primary etiologic agent and it exists in a state of biofilm

- Plaque contains microorganisms which provoke inflammatory reaction from the host leading to connective tissue destruction, pocket formation and bone loss.

- Treatment options include surgical and non-surgical periodontal therapy

- Since periodontal pathogens reside inside the tissues, use of antimicrobials as adjunct to scaling and root planning is highly recommended.
- Antimicrobials can be delivered locally and systemically.
- Use of local drug delivery systems for treating periodontitis offers several advantages.

- Removal of this biofilm by mechanical instrumentation is essential

Limitations : (*Quirynen et al 2002*)

- unfavorable anatomy of the tooth
- presence of tissue invasive organisms
- bacterial invasion into dentinal tubules

- To overcome this, **Antimicrobials both systemic and locally acting were used as adjuncts to mechanical therapy**
- Systemic antimicrobial agents may reduce or eliminate bacteria that cannot be removed by scaling and root planning.

ADVERSE EFFECT OF SYSTEMIC ANTIMICROBIALS

- drug toxicity
- drug interaction
- acquired bacterial resistance
- Patient compliance

- Dr. Max Goodson (1979) developed local delivery of therapeutic agents into a viable concept.
- **Local delivery of antibacterial agents into periodontal pocket**

  -limiting the drug to its target site

  - Achieve high concentration at target site

HISTORY

- **W.D. Miller 1880** the use of an antimicrobial mouth rinse (Listerine) to aid in fighting what was then known as ‘Pyorrhea alveolaris’.
- **Dr. Max Goodson 1979** championed and developed controlled release local delivery of therapeutic agents.

OBJECTIVES

- The use of a local antimicrobials is to prevent or control microbial induced inflammation in an effective concentration and be maintained there for long enough for the desired effect to be accomplished without causing any diseases.

ADVANTAGES

- LDD can attain100 folds higher concentrations of the agent in sub gingival sites compared with a systemic drug regimen
- LDD may employ antimicrobial agents not suitable for systemic administration such as various broad spectrum antiseptic solutions (eg: CHX)

- Personally applied antimicrobial regimens offer the potential of daily placement into pockets for complaint patients
- Professionally applied antimicrobial regimens reduce potential problems with patient compliance

INDICATIONS

- Isolated Periodontal Pockets (>5mm), with Successful phase 1 therapy
- Periodontal patients who are medically Compromised where surgical therapy is contraindicated.
- In combination With Mechanical Debridement who are suffering from Recurrent periodontitis.
- During periodontal regenerative procedures.

CONTRA-INDICATIONS

- with known Hypersensitivity reaction to Antimicrobials
- Those requiring multiple areas of treatment.
- As replacement or SRP, replacement for Surgical therapy.
- asthmatics, Infective conditions (AIDS,TB)

DISADVANTAGES

- Difficulty in placing into deeper parts of pockets and furcation lesions.
- Patient compliance and manual dexterity.
- Time consuming and labour intensive inpatients with numerous advanced lesions.
- Do not markedly affect pathogens residing on extra-pocket oral surfaces.
- Non-sustained drug delivery provides only a brief exposure of the target microorganism to the applied antimicrobial agent.

Difference Between Systemic And Local Antimicrobials

	Systemic	Local
1. Route of administration	Oral or Parental	Site Specific
2. Pain/Discomfort	Not painful	Nil
3. Drug dosage	Higher drug dosage (in mg)	Lower dosage (in micrograms)
4. Peak levels	Few hours in plasma	Within few minutes in GCF
5. Pharmacokinetics	Distribution in various compartments where antimicrobial effect may not be required.	Minimal body distribution to different compartments with maximum concentration at delivered sites.
6. Frequency	Once in 6-12 hours	Usually once a week
7. Super infection	Present	Limited
8. Microbial resistance	Present	Limited

	Systemic	Local
9.Patients compliance	Required for better efficacy	Patient delivered - compliance required Professional Delivered - not required
10.Time required	Less time	Longer time if many sites are involved
11. Side effects	More	Limited
12. Effects on connective tissue associated plaque	Effective	Limited

Ideal Requirements For Local Antimicrobial Agents: *(Goodson 1985)*

- Must deliver the drug to the base of pocket.
- Must have microbiologically effective concentrations in the pocket.
- Should sustain the concentration of the drug in the pocket for sufficient period of time & at a concentration to be clinically effective.
- Less undesirable side effects.

CLASSIFICATION OF LOCAL ANTIMICROBIAL THERAPY IN PERIODONTICS

1. **based on their mechanism of action (Langer & Peppas (1988)**

- Diffusion controlled systems
- Chemically controlled systems
- Solvent activated System
- Release induced by external forces

- **Solvent activated System**

- Osmotic system

- Swelling controlled system

- **Release induced by external forces**

-Magnetically controlled systems

2. depending on the type of therapy (Rams & slots 1996)

- **PERSONALLY APPLIED (In patient home self-care**)

✓ Non-sustained Subgingival Drug Delivery

✓ Sustained Subgingival Drug Delivery

- **PROFESSIONALLY APPLIED (In dental office)**

3. Based on duration of action (Greenstein & Tonetti 2000)

A) SUSTAINED RELEASE DEVICES

- Drug delivery for less than 24 hrs require multiple applications

B)CONTROLLED DELIVERY DEVICES

- Duration of drug release exceeds 24hrs administered once

4.based on degradability

i. non degradable (1st gen)

ii. degradable (2nd gen)

VARIOUS DRUG DELIVERY DEVICES :

- FIBERS
- FILMS
- INJECTABLE GELS
- STRIPS AND COMPACTS
- VESICULAR LIPOSOMAL SYSTEMS
- MICROPARTICLE SYSTEM
- NANOPARTICLE SYSTEM

Fibers

- Fibers or thread-like devices are reservoir-type systems, placed circumferentially into the pockets with an applicator and secured with an adhesive for the sustained release of the trapped drug into the periodontal pocket.

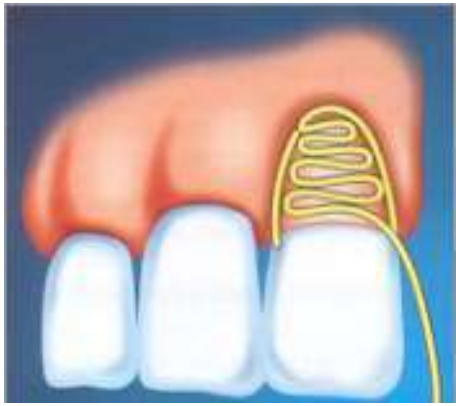
2 types

1. hollow- reserviours without rate control system drug release-diffusion.

   Eg: tetracycline in hollow fibres of cellulose acetate

2.Monolithic- controlled dug release.

(monolithic fibres of EVA with 25% tetracycline HCl)



- Several polymers like Polyethylene, Polypropylene, Polycaprolactone, Polyurethane, Cellulose acetate propionate and Ethylene vinyl acetate (EVA) have been investigated as matrices for LDD.
- Eg: Chlorhexidine fibres, tetracycline fibres.

Films

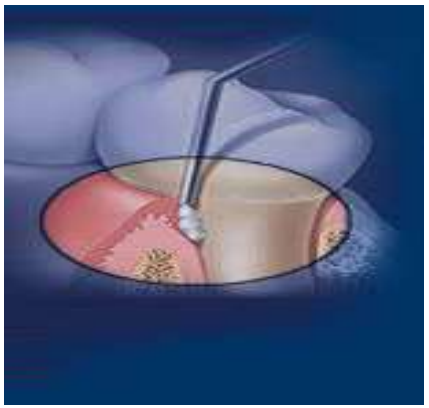
- Films are matrix delivery systems in which drugs are distributed throughout the polymer and release occurs by drug diffusion and/or matrix dissolution or erosion.
- Bigger films could be applied within the cavity onto the cheek mucosa or gingival surface

- Both degradable and non- degradable films are available.

Advantages

- Could be cut or punched into appropriate sizes so as to be inserted into the site of action.
- Can be easily inserted
- Minimal discomfort to the patient
- Sufficient adhesiveness is present

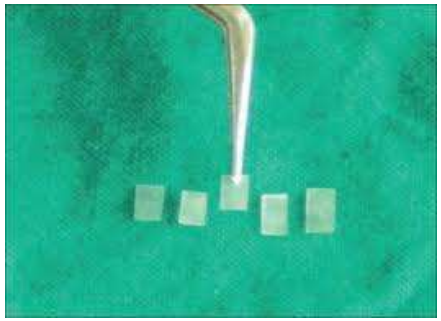
- **Non degradable films(**Addy et al-1982 **)** described the film or slab form intrapocket delivery devices.
- They described the use of slabs made of methyl methacrylate for the intrapocket delivery of tetracycline, metronidazole, chlorhexidine .
- **degradable devices ,Periochip controlled subgingival delivery of chlorhexidine.**



Injectable System

- It is relatively simple procedure.
- fluid nature of the formulations would allow the drug to gain access to the entire pocket.
- The application can be easily and rapidly carried out without pain by using a syringe.
- The formulation undergo a change in to a sticky semisolid or solid phase so as to prevent it from being washed out.

- A higher biocompatibility and bio-adhesivity, allowing adhesion to the mucosa in the dental pocket.
- They can be rapidly eliminated through normal catabolic pathways, decreasing the risk of irritative or allergic host reactions at the application site.
- Eg: gel formulations of tetracycline (2.5%), metronidazole (25%), metronidazole benzoate (40%), combination of tetracycline (2.5%) and metronidazole benzoate (40%).



Strips and Compacts

- Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of antimicrobial agents.
- Strips containing tetracycline, metronidazole or chlorhexidine demonstrated a decrease in number of motile rods, notably spirochetes.
- In a later development, the evaluation of amoxycillin- clavulanic acid loaded acrylic strips is reported.

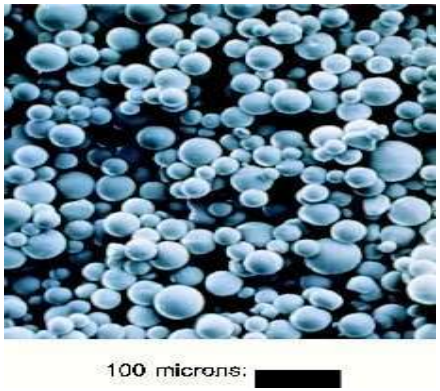
- Highest level of antibacterial agent was released during the first 24 hours period followed by release of therapeutic level of drugs for a subsequent 9 days period.
- Effect persisted even after 3 week of removal of acrylic strips.
- Tissue adhesive implants were made using n-butyl-2-cyanoacrylate as a drug trapping material and slowly release drug when used in the form of a biodegradable local drug delivery device.

Vesicular Systems

- Designed to mimic the bio-membranes in terms of structure and bio behaviour and hence are investigated intensively for targeting periodontal biofilms
- The targeting of liposomes was thought to be because of the interaction of the polyhydroxy groups of liposomes with surface polymers of the bacterial glycol-calyx.

- Proteo liposomes have been found to be effective for the delivery of triclosan to periodontal biofilms.
- **Robinson et al** Even after a very short exposure, liposome's were retained in the bacteria delivering the drug into cellular interiors.

Micro particle System



- Non-biodegradable and biodegradable materials for the preparation of microspheres include the polymers of natural origin, modified natural substances and synthetic polymers.
- Biodegradable polymers such as poly lactide (PLA) or poly (lactide – co-glycolide) PLGA has been designed for periodontal disease therapy.

- PLGA microspheres containing minocycline have been used for the elimination of Porphyromonas gingivalis from the periodontal pocket.
- provide stability to the encapsulated drug.
- The in vitro drug release in these systems depends upon the polymer (lactide: glycolide) ratio, molecular weight, crystallinity and pH of the medium.

Nanoparticle System

- The nanoparticulate system provides several advantages as compared with microspheres,
- microparticles and emulsion-based delivery systems, including high dispersibility in an aqueous medium, controlled release rate and increased stability.
- Penetrate regions that may be inaccessible to other delivery systems, such as the periodontal pocket areas below the gum line

- These systems Reduce the frequency of administration and Provide a uniform distribution of the active agent over an extended period of time.
- Biocompatible nanoparticles composed of 2-hydroxyethyl methacrylate (HEMA) and polyethyleneglycol dimethacrylate (PEGDMA) could be used as a drug delivery system for dental applications.

- Three preliminary studies -assess the efficacy of nanoparticles in periodontal drug delivery.

a) Dung et al-Antisense oligonucleotide- loaded chitosan tripolyphosphate (TPP) nanoparticles and showed the sustained release of oligonucleotides which is suitable for the local therapeutic application in periodontal diseases

b) Pinon et al- An in vivo study in dogs with induced periodontal defects using Triclosan-loaded polymeric (PLGA, PLA and cellulose acetate phthalate) nanoparticles and suggested that triclosan-loaded nanoparticles penetrate through the junctional epithelium

c) Moulari et al- the in vitro bactericidal activity of the Harungana madagascariensis leaf extract (HLE) on the oral bacterial strains largely implicated in dental caries and gingivitis infections

- Incorporation of the HLE into a colloidal carrier improved its antibacterial performance and diminution of the bactericidal concentration was observed.

Commercially Available Products

- **Tetracycline fibers** (Actisite, Alza Corp., Mountain view, California)
- **Minocycline ointment** (Dentomycine, Lederle, UK & Periocline, Sunstar, Japan)
- **Doxycycline hyclate** in a resorbable polymer (Atridox, Atrix Labs, CO)
- **Metronidazole gel** (Elyzol, Dumex, Copenhagen, Denmark)
- **Chlorhexidine Chip** (Perio chip Peno Products Ltd., Jerusalem, Israel)

TETRACYCLINE

- Tetracycline is a bacteriostatic antibiotic that interferes with bacterial protein synthesis and inhibits tissue collagenase activity.
- Agents used commonly are: Tetracycline HCl, Doxycycline HCl, Minocycline HCl
- Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis.
- The first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline.

- Tetracycline containing fibers (Actisite)
- Non resorbable, biologically inert, safe polymer (ethylene vinyl acetate) loaded with 25% tetracycline HCl powder packed as flexible yellow fibres of 0.5mm d, 23cm length (2.7 mg TTC).
- maintains constant concentrations of active drug in the crevicular fluid in excess of 1000 µg/mL for a period of 10 days Maurizio S et al
- In contrast GCF conc. of only 4-8 microgram/ml were reported after systemic administration 250 mg qid for 10 days.

Other forms

- Recently Bioresorbable form is PERIODONTAL PLUS AB formulation containing TTC (2 mg of Tetracycline) in 25 mg of collagen fibrils.
- dual mode of action by enables the active agent and vehicle to be able to work positively towards the repair of the periodontal lesion.
- Each vial contains 25 mg (Total 100 mg in 4 vials)

- Tetracycline-Serratiopeptidase-Containing Periodontal Gel
- **Maheshwari et al** - Serratiopeptidase tetra gel with aerosol (colloidal silica) used. Aimed to decrease polymer concentration and to obtain reasonable viscosity at a lower concentration of pluronic gel by adding a viscosity modifier.
- Results -Formulation has shown statistically significant results along with scaling and root planning

- **Goodson et al-** In a 60-day multicenter study - 107 periodontitis patients after supragingival scaling
- Four non-adjacent teeth (pockets in the range of 6-10mm) was selected and randomly assigned to 4 groups-Tetracycline fiber, Placebo fiber, Scaling and Untreated.
- Results-fiber therapy significantly had reduction in probing depth, BOP and gain in attachment levels

- **Newman et al 1994-** in periodontal maintenance patients needing treatment of localized recurrent periodontitis effect of fiber therapy was evaluated as an adjunct to SRP.
- Results – sites treated with fiber and SRP showed significantly higher attachment level, pocket depth reduction and less BOP.

- Singh *et al 2009- 3* months -No difference in the results achieved with local tetracycline hydrochloride or local metronidazole as adjuncts to mechanotherapy.
- Sadaf *et al 2012-3* months-Higher reduction in plaque index, gingival index and in the clinical probing depths of the tested group than of the control group at all time intervals -15, 30, 60 and 90 days.
- Gupta et al.*2015* - more reduction in clinical parameters (PD,GI, PI) compared to control

SUBGINGIVAL DOXYCYCLINE

- broad-spectrum antibioti bacteriostatic, inhibiting bacterial protein synthesis ability to downregulate MMPs.
- The only FDA approved 10% Doxycycline – **ATRIDOX gel (42.5 mg Doxycycline)**
- Subgingival controlled-release product composed of a 2 syringe mixing system.

2 syringe mixing system

- Syringe A -450 mg of the ATRIGEL® Delivery System, which is a bioabsorbable, flowable polymeric formulation.
- Syringe B- doxycycline hyclate which is equivalent to 42.5 mg doxycycline.

- The constituted product is a pale yellow to yellow viscous liquid with a concentration of 10% of doxycycline hyclate.
- Upon contact with the crevicular fluid, the liquid product solidifies and quickly hardens to a wax like substance, then allows for controlled release of drug for a period of 7 days.

- **Garrett et al 2003 -**Treatment to be statistically superior to placebo control and oral hygiene and equally effective as SRP.
- **Machion L et al 2006-**Reduction in clinical parameters use of locally delivered doxycycline may constitute an important adjunct for the active and supportive treatments of severe periodontal disease in smokers.
- **Deo et al (2011)-**significant reductions in PPD and gains in CAL compared to SRP alone.

SUBGINGIVAL MINOCYCLINE

- Semi synthetic tetracycline - first introduced in 1967 in vitro antibacterial activity against a wide range of gram-ve and gram +ve microorganisms
- LDD minocycline - tried clinically via in three different modes such as **film, microspheres, and ointment.**

Film

- Ethyl cellulose film containing 30% of Minocycline were tested as sustained release
- complete eradication of pathogenic flora from the pocket after 14 days.

Microsphere:

- Locally delivered, sustained release form of minocycline microspheres (ARESTIN) for subgingival placement is available.
- Arestin- 2% minocycline encapsulated into bio-resorbable microspheres (20-60µm in diameter) in a gel carrier and has resorption time of 21 days.
- Gingival crevicular fluid hydrolyses the polymer and releases minocycline for a period of 14 days or longer before resorbing completely.

Ointment:

- 2% minocycline hydrochloride in a matrix of hydroxyethyl-cellulose, aminoalkyl-methacrylate, triacetine & glycerine.
- DENTOMYCIN –European union PERIOCLINE - JAPAN
- The concentration of minocycline in the periodontal pocket is about 1300µg/ml, 1 hr after single topical application of 0.05 ml ointment (1mg of minocycline) and is reduced to 90µg/ml after 7 hrs.

- **The Dentomycin gel** has been reported to be effective in periodontal disease because of
- Its power to eliminate key periodontal pathogens.
- Minimal risk of bacterial resistance.
- Inhibits harmful bacterial collagenase without effecting normal collagen turnover and regeneration of gingival tissues

- Van Steenberghe et al 1993-a significantly greater reduction of PD in test group- Treatment to be statistically superior to control
- Jung et al 2012-Reductions in PPD, BOP and gain in CAL were significantly greater at the minocycline ointment in association with flap surgery site than at the flap surgery site alone.
- Pandit N , et al 2013-that treatment with Minocycline microspheres and Metronidazole gel improve PPD and CAL in patients with periodontitis compared to SRP alone.

CHLORHEXIDINE

- Available as mouthrinses, Gels, varnishes, and chip to be used as a local drug delivery agent .

MECHANISM OF ACTION (Rolla and Melsen)

- By binding to anionic acid groups on salivary glycoprotein thus reducing pellicle formation and plaque colonization.
- By binding to salivary bacteria and interfering with their adsorption to teeth.

- Chlorhexidine has been shown to be an effective agent in plaque inhibition (Loe et al 1976) as well retained in the oral cavity,
- Reacting reversibly with receptors in the mouth due to its affinity for hydroxyapetite and acidic salivary protein.
- Its antibacterial action is due to an increase of the cellular membrane permeability followed by the coagulation of intracellular cytoplasmic macromolecule.

Periochip:

- Small chip (4.5× 3.5mm) composed of biodegradable hydrolyzed gelatin matrix, crosslinked with glutaraldehyde, also contains glycerine & water into which chlorhexidine gluconate (2.5mg) is incorporated.
- Perio Chip releases chlorhexidine in vitro in a biphasic manner,
- Initially releasing approximately 40% of the chlorhexidine within the first 24 hours, and then releasing the remaining chlorhexidine in an almost linear fashion for 7–10 days.

Periocol-CG:

- Periocol CG is prepared by incorporating 2.5mg chlorhexidine from a 20% chlorhexidine solution in collagen membrane.
- Size of the chip is 4x5 mm and thickness is 0.25 - 0.32 mm and 10 mg wt.

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

- Grover et al 2011- in a clinically significant improvement in PPD and CAL compared with SRP alone.
- Medaiah et al 2014-No statistically significant differences between SRP and SRP + CHIP group in all clinical parameters

SUBGINGIVAL METRONIDAZOLE

- Metronidazole is particularly attractive as an antimicrobial because of its selective efficacy against obligate anaerobes.
- Both systemic and local applications are effective against periodontal pathogens.
- Metronidazole has been incorporated as collagen sponges, dialysis tubing, acrylic strips, films and gel forms for sustained subgingival delivery in the treatment of periodontal disease.

Elyzol

- metronidazole 25% in a mixture of glyceryl mono-oleate and sesame oil.
- Contains metronidazole benzoate- active agent.
- flows freely on application on contact with gingival crevicular fluid becomes more viscous and stays in the periodontal pocket gel disintegrates in the pocket and releases metronidazole.
- for at least 24 hours Can be administered quickly and easily and high periodontal pocket levels of metronidazole are maintained.
- Administered twice- with an interval of one week.

- Griffiths et al 2000-Combined therapy of SRP and metronidazole 25% dental gel was superior to the conventional treatment of SRP alone

NEWER TRENDS IN LOCAL DRUG DELIVERY

- Drugs For Osseous Defects
- Alendronate- a novel bisphosphonate very potent inhibitor of bone resorption.
- **Anuj Sharma et al, 2011-** local delivery of 1% ALN into periodontal pockets as an adjunct to SRP stimulated a significant increase in PD reduction, CAL gain, and improved bone fill

- **Statins– Simvastatin, Atorvastatin, Rosuvastatin**
- Lipid lowering drugs-- an effective approach for the treatment of hyperlipidemia and arteriosclerosis.
- Statins are specific competitive inhibitors of HMG-CoA reductase.
- modulate bone formation by increasing the expression of bone morphogenetic protein-2, inflammation and angiogenesis.

- **Pradeep et al 2010** – A greater decrease in gingival index and probing depth and a clinical attachment level gain with significant defect fill at sites treated with scaling and root planing plus locally delivered SMV gel
- Reduction in PD, CAL gain and greater mean percentage of radiographic bone fill ATV as an adjunct to SRP can provide a new direction in the management of IBDs.

- AR Pradeep 2016-LDD of 1.2% RSV results in significantly greater clinico-radiographic improvement than 1.2% ATV or placebo gels as adjunct to mechanical periodontal therapy

HERBAL PRODUCTS FOR PERIODONTITIS

- Eucalyptus Extract
- Neem Leaf
- Bloodroot
- Chamomile
- Liquorice
- Propolis
- Aloevera

Conclusion

- There is ample evidence to show that locally delivered antimicrobials can reduce clinical and microbial parameters to a level, if not better than at least comparable to that of scaling and root planing.
- Mechanical instrumentation, can be technically demanding, time consuming, and in some periodontal defects ineffective or incomplete.

- LDD on the other hand is simple to use and may conceivably in the future be delivered by the patient themselves, hence can be used as an adjunct to mechanical plaque removal.
- local drug delivery though not a substitute for the conventional therapy, can be of added benefit if used as an adjunct with the conventional scaling and root planning.

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- Thank u….