LITERATURE REVIEW

Subhas G\(^5\) (2010), reported that the periodontal diseases are major cause of tooth loss during adulthood of population irrespective of sex and age. Various treatment modalities have been available to the dental profession. Scaling polishing along with self administered plaque control instructions is the most commonly practised by general dentist for prevention and control of early periodontal diseases. Root planning and soft tissue curettage procedures are added to it for treatment of moderate type periodontal diseases. In some cases, it has limited success and therefore, local applications of some antibacterial drugs by topical application or local drug delivery in the periodontal pockets have been tried. Periodontal pockets provide natural reservoir bathed by gingival crevicular fluid that is easily accessible for the insertion of a delivery device. Controlled release delivery of antimicrobials directly into periodontal pockets has received great interest and appears to hold a sound promise in periodontal therapy. Both topical drug delivery and controlled drug release have been termed as local drug delivery. The periodic use of local drug delivery in minimizing bleeding, stabilizing attachment levels and thereby reducing probing depth, would allow better control and management of periodontal disease.

Swati R, Sandeep W, et al\(^6\) (2010), developed biocompatible and biodegradable syringeable \textit{in-situ} gel formulation of Ornidazole having controlled release characteristics for direct placement into the periodontal pocket using Poloxamer 407(Pluronic F-127) to inject without incision. Ornidazole specifically acts on gram negative anaerobic, facultative bacteria which are responsible for periodontal disease. Ornidazole requires a very low minimum inhibitory concentration to inhibit the growth of periodontal pathogens as compared to that of Metronidazole. \textit{In-vitro} drug release showed that formulation containing 20% Pluronic F-127 released the drug completely within 8 hour. For \textit{in-vitro} antibacterial activity, isolation, characterization, and identification of bacterial strain were carried out from dental plaque sample collected from Periodontal diseased patients. The antibiotic assay of Ornidazole gel was performed against \textit{E.coli}, \textit{S.aureus} and isolated coagulase negative \textit{Staphylococcus spp.} \textit{In-vitro} antibacterial study showed higher zone of inhibition as compared to marketed formulation. The results of study indicate that, Pluronic F-127 is promising polymer to develop \textit{in-situ} gel formulation for periodontal disease.
Ananta C, Sujoy D, et al\textsuperscript{7} (2010), designed a sustained release film formulation of ciprofloxacin hydrochloride for the treatment of periodontal diseases and investigate different experimental parameters. Films were formulated using different concentration hydroxypropylmethyl cellulose and polyvinyl alcohol. The prepared films were subjected to different evaluation like determination of weight, thickness, surface pH, folding endurance, swelling index, mucoadhesion time, mucoadhesion strength, drug content, invitro drug release study, ex-vivo release study and release kinetic behavior. From the results of evaluation it was concluded that all the prepared films having desire flexibility and mucoadhesive properties, along with that they shows good in-vitro and ex-vivo drug release performance. Drug release from the films follows desire sustained release phenomenon as needed in buccoadhesive drug delivery.

Jongjan M, Juree, et al\textsuperscript{8} (2010), formulated gels containing Zink oxide for the treatment of periodontitis, and thus for practical purposes. ZnO was studied as the main compound and xanthan gum was used as the gel-forming agent. The effects of clove oil and eugenol added into the prepared gel were studied. The prepared gels were evaluated in terms of their gel properties including viscosity, pH and antimicrobial activity. The viscosity of the prepared gel was increased as the concentrations of xanthan gum, ZnO, clove oil and eugenol were increased. The antimicrobial activity of the prepared gel was increased when the concentration of clove oil and eugenol was increased. The antimicrobial activity of systems comprising clove oil tended to be higher than that of eugenol.

Bansal K, Rawat M et al\textsuperscript{9} (2009), formulated satranidazole-containing mucoadhesive gel for the treatment of periodontitis. Different mucoadhesive gels were prepared, using various gelling agents like sodium carboxymethylcellulose (SCMC), poloxamer 407, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and the mucoadhesive polymer carbopol 934P. The selected formulations were studied for different mechanical properties, such as mucoadhesive strength, hardness, compressibility, adhesiveness, and cohesiveness through Texture Profile Analyzer. In vitro satranidazole release from the prepared formulations was also determined and compared with marketed preparation of metronidazole (Metrogyl\textsuperscript{®} gel). The formulation containing SCMC 3% w/v showed maximum mucoadhesive strength (167.72 ± 3.76 g) and adhesiveness (−46.23 ± 0.34 Nmm), with low hardness (9.81 ±
0.04 N) and compressibility (40.05 ± 0.48 Nmm) and moderate cohesiveness (0.87 ± 0.01). formulation exhibited long-term release. Thus, this gel was evaluated for its clinical effectiveness along with marketed metronidazole gel. At the end of the study (42 days of clinical studies), both formulations were found to significantly reduce the probing depth, plaque index, gingival index, calculus criteria, and bleeding index.

**Pragati S, Ashok S, et al** (2009), Reported that the relationship between bacterial plaque and the development of periodontal disease and caries is well established. 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. Systemic administration of drugs leads to therapeutic concentrations at the site of infection, but for short periods of time, forcing repeated dosing for longer periods. Local delivery of antimicrobials has been investigated for the possibility of overcoming the limitations of conventional therapy. The use of sustained release formulations to deliver antibacterials to the site of infection (periodontal pocket) has recently gained interest. These products provide a long-term, effective treatment at the site of infection at much smaller doses. Biodegradable polymers are extensively employed in periodontal drug delivery devices because of their abundant source, lack of toxicity, and high tissue compatibility. A major advantage of natural polymers is that they do not affect periodontal tissue regeneration. Amongst various natural polymers, chitosan, a deacetylated product of chitin is widely used in drug delivery devices. Since it exhibits favourable biological properties such as non-toxicity, biocompatibility, biodegradability and wound healing traits, it has attracted great attention in the pharmaceutical and biomedical fields.

**Mastiholimath V, Dandagi P, et al** (2006), developed for site-specific one-time continuous delivery of ornidazole an antimicrobial compound with excellent activity against anaerobic microorganisms in the treatment of periodontal infections as dental implant. The dental implant was prepared by solvent coating technique using ethyl cellulose, HPC, HPMC K4M and Eduragit RL-100 with dibutyl phthalate as plasticizer. The drug release was initially high on day one to achieve immediate therapeutic level of drug in pocket, followed by marked fall in release by day two, and progressive moderate release profile to maintain therapeutic level.
Alka A, Ali J, et al\textsuperscript{12}(2006), developed targeted retentive device for the treatment of periodontal infections containing Amoxicillin Trihydrate. Nylon fibers were taken as core materials. The coating solution contained polyvinyl acetate and amoxicillin trihydrate. The fibers were coated five times to maximize drug loading. The coating composition was optimized and fibers were subjected to in vitro release studies. The drug release followed first order release and Fickian diffusion mechanism. The retentive fibers shown to provide controlled delivery of amoxicillin trihydrate.

Giuseppe and Perinetti\textsuperscript{13} (2004), performed controlled single blind study to assess and compare the clinical healing and microbiological findings following repeated intrasulcular application of 1% metronidazole or 1% chlorhexidine gels in persistent periodontal pockets previously treated by scaling and root planning. Systemically healthy subjects, 25 males and 38 females diagnosed for chronic periodontitis were enrolled in this study. Three month later at baseline a single persistent pocket with a probing depth of 59 mm was chosen as the experimental site in each patient. The treatment consist of four repeated as administration of subgingival gel, each separated by seven days, starting at a baseline, subgingival plaque were sampled from experimental site at baseline, prior to first gingival administration and at 7, 15, 30 and 90 days after the end of the treatment. PD was significantly by the same amount in all experimental groups. In the subgingival administration of MG or CG, both at 1% may have a role in the management of persistence pockets during chronic periodontitis.

Perugini P, Genta I, et al\textsuperscript{14}(2003), developed monolayer composite systems made of ipriflavone loaded poly(d,l-lactide-co-glycolide) (PLGA) micromatrices in a chitosan film form, were obtained by emulsification/casting/evaporation technique. Multilayer films, made of three layers of polymers (chitosan/PLGA/chitosan), were also prepared and compared to monolayer films for their “in vitro” characteristics. Morphology and physico-chemical properties of the different systems were evaluated. The influence of pH, ionic strength and enzymatic activity on film degradation, was also investigated. Significant differences in swelling, degradation and drug release were highlighted, depending on film structure and composition. In vitro experiments demonstrated that the composite micromatricial films represent a suitable dosage form to prolong ipriflavone release for 20 days.
Nagaraju R, Udupa N, et al\textsuperscript{(2003)}, formulated dental implants of tinidazole using Poly (ε-caprolactone), a biodegradable, polymer. Clinical study was carried out to evaluate the usefulness in periodontal therapy. Gingival crevicular fluid concentration of the drug was found to be $4.9 \pm 3.2$ mcg per mg of gingival fluid which was higher than the minimum inhibitory concentration for many of the periodontal pathogens throughout the period of study (40 days). Low drug concentration was found in saliva, which is desirable. High concentration of drug in saliva may suppress the normal commencial flora of the oral cavity and may also pose a risk of cover growth of opportunistic organisms causing several adverse effects. The implants prepared were capable of releasing tinidazole and maintain effective concentration in gingival crevicular fluid for an adequate duration of time to inhibit the growth of various periodontopathic organisms, which confirms the clinical efficacy of the implants prepared.

Sharma N, and Galustains H\textsuperscript{(2003)}, performed antiplaque/antigingivitis efficacy of a hexidine containing mouthwash. Subjects were randomly assigned to one of three mouthwashes (hexidine 0.1%, chlorohexidine 0.12% (Positive control) or a 5% hydroalcohol negative control) and commenced three times daily supervised rising as their sole method of oral hygiene. All indices were recorded after 2 weeks. Compared to the negative control group, the hexidine group demonstrated a statistically significant inhibition and reduction of supra-gingival plaque and gingival inflammation with reduction of 6.3%, 33.5% and 56% for gingivitis, plaque and gingival bleeding, respectively. The results of the chlorohexidine group were used to validate the study. The study confirmed the efficacy of a hexidine rinse in reducing supra-gingival plaque and gingival inflammation.

Behnen and Michael J\textsuperscript{(2001)}, evaluated the antimicrobial activity of several calcium hydroxide [Ca (OH)\textsubscript{2}] preparations in root canal dentin infected with enterococcus faecalis. There were five treatment groups 1, a thick mixture of Ca (OH)\textsubscript{2} USP (1.0 g/ml H\textsubscript{2}O). Group 2, a thin mixture of Ca (OH)\textsubscript{2} USP (0.1 g/ml H\textsubscript{2}O), groups 3, pulp dent temp canal TM paste, group 4, sterile H\textsubscript{2}O (positive control) and group 5,25 dentin specimens in sterile, uninoculated brain-heart infusion broth that were included as negative controls. Quantitative microbiological analysis of dentin at various depths was completed after 24 hr all groups showed a significant (P < 0.001) decrease in
numbers of E. faecalis in all depths of dentin compared with the control. Groups 2 and 3 demonstrated significantly greater antimicrobial activity (73%-86% reduction) at all depths of dentin tested compared with group 1 (13%-26%). These results suggest that Ca (OH)$_2$ can decrease the numbers of E. faecalis at all depths of dentinal tubules within 24 hr and that thin preparation of Ca (OH)$_2$ may be more effective in the elimination of E faecalis from dentinal tubules than thick preparation. In periodontal therapy controlled release devices containing tetracycline, doxycycline monocyline, metronidazole, tinidazole, chlorhexidine, ofloxacin, ciprofloxacin etc., were developed and extensively investigated for their usefulness.

**Karnik A and vania P** (2001), demonstrated that the Periodontitis is a inflammation of the gum, it is a result of poor oral hygiene. Doxacycline hydrochloride is a highly potent antibiotic belong to the class of tetracycline recommended for the treatment of the periodontitis. The aim of this work to archive stable injection of stable gel-sol of DOX, which would cause sustained released of DOX. Currently available DOX injection has to be induced after every 4-5 hours which is very inconvenient; hence we have attempted to develop novel gel-sol injection of DOX. Lutrol in water at room temperature remain in liquid state where as at body temperature it converted in to thick gel form so that lutrol was used for the formulation of gel-sol injection of DOX.

**Kargill B and Kadir T** (2001), investigated the antibacterial effect of a sort term topical application of ornidazole on anaerobic microorganisms. The antibacterial properties of such materials against organisms at infected primary root canal have not been well documented; twenty infected primary morals in this study were treated using ornidazole. The bacterial contents of the root were collected in sterile paper. Freshly mixed ornidazole and sterile saline were placed into the root canals. After one week, the bacterial content of root canal collected again. Microbiological analysis were made. Based on our result it appears that the anti bacterial activity of ornidazole causes significant changes in rates of microorganisms.

**Vyas S, Shiorkar V, et al** (2000) determined the etiology, epidemiology, pathogenesis, and microbiology of periodontal pocket flora and revolutionized the strategies for the management of intraperiodontal pocket disease. Intra pocket, sustained release drug delivery devices have been shove to be clinically effective in the periodontal infections. Several degradable and nondegradeble devices are under
investigation for the delivery of antimicrobial agent into the periodontal pocket. Intraperiodontal pocket drug delivery has emerged as a paradigm for future research. Similarly bioadhesive systems are explored that could significantly improved oral therapeutics for periodontal disease and mucosal lesion. A strategy is to target a wide range of molecular mediators of tissue destruction and hence arrest periodontal disease progression.

Reinhardt R, Maze G, et al \(^{(1995)}\), determined tetracycline level in gingival crevicuar fluid from periodontitis sites treated with a simple placement of tetracycline lactic glycolic acid bioerodible gel system (high viscosity gel and low viscosity gel) over a 4 day period. 90% of the sites receiving the gels had more than 100 mcg tetracycline per ml of gingival crevicular fluid at the end of the day.

Giordano J, and Loasche W \(^{(1995)}\), evaluated the effect of local delivery of antimicrobial agents and systemic antimicrobials. Films containing 20% metronidazole, 20% chlorohexidine or placebo was inserted into periodontal pockets for 2 weeks with a change of film after the first week. The results suggested that the local delivery of antimicrobial agents plus scaling and root planning could result in reduction in surgical needs for teeth refractory to initial treatment.

Walker C, Mangnusson I, et al \(^{(1995)}\) confirmed the studies of other investigators that, sustained delivery system containing metronidazole produce 75% decrease in total microbial count and can achieve a shift in the microbial patterns to a gram-positive cocci dominace, which is generally considered to be associated with good health.

Polson A, Garrett S, et al \(^{(1995)}\), compared the efficacy of 10% doxycycline hyclate with 5% saguinarine chloride contained within a polymer delivery system. The investigation established that treatment with sub gingival doxycyclin using the polymer delivery system improved and maintained periodontal health significantly better than other treatment.

Lehman B, Mombelli A, et al \(^{(1995)}\), studied the clinical response to local delivery of tetracycline in relation to overall condition of the other teeth. A two months study concluded by demonstrating the improvement of various clinical parameters. Drisko CL, and Charles M, Cobb \(^{90}\), evaluated the clinical efficacy of controlled release
tetracycline fiber therapy in 122 adult periodontitis patients. Results showed that treatment resulted in improvement in clinical parameters.

**Killoy J, Rapely W, et al** (1995), compared the effect of controlled local delivery of tetracycline (Actisite) received every six months to routine periodontal maintenance treatment (scaling, local root planning and polishing) received every three months. The result showed that the controlled delivery of tetracycline therapy was significantly more effective than routine maintenance therapy.

**Drisko C, and Charles M** (1995), evaluated the clinical efficacy of controlled release tetracycline fiber therapy in 122 adult periodontitis patients. Results showed that treatment resulted in improvement in clinical parameters.

**Subuski D, Asthon P, et al** (1994), evaluated sustained release of tetracycline and ciprofloxacin. Efficacy of lipophilic membrane composed of polylactic acid (PLA) and a hydrophilic membrane composed of poly vinyl alcohol (PVA) were investigated. Results demonstrated that the lipophilic membrane (PLA) provided significantly longer sustained release when compared to the hydrophilic membrane (PVA), which released both the drugs within the first 24 hours. The polylactic acid membrane (PLA) provided sustained drug release over the 14th day period of observation.

**Jones A, Korrman K, et al** (1994) evaluated the clinical effects of controlled release locally delivered minocycline in 51 patients with periodontitis. They concluded that minocycline delivered subgingivally in a biodegradable polymer may provide significant benefit in reducing pocket depth. The above 3 studies assuring tetracycline, doxycyclin and minocycline sustained release therapy have confirmed the biological rational for using sustained local drug delivery device. Preliminary data suggest that sustained delivery of these drugs combined with scaling and root planning may provide benefit beyond scaling and root planning alone in patients who have sites that are unresponsive to conventional therapy.

**Lowenguth RM, and Gandini L** (1993), evaluated the effectiveness of periodontal treatment with ethylene vinyl acetate fibres containing 25% tetracycline hydrochloride. Treatment resulted in the decrease in pocket depth and probing attachments level at 2 months post treatment when compared to control group where no treatment given. Analysis of the tetracycline concentration within gingival crevicular fluid demonstrated
that tetracycline was primarily confined to the sites that received fibre therapy. They concluded that local delivery of tetracycline with scaling was most effective in localised juvenile periodontitis.

Kazakos G, Cobb C, et al\textsuperscript{11}(1993), evaluated the antimicrobial effects of monolithic tetracycline impregnated fibres. Results indicated that use of these fibres over a ten-day period did not adversely affect the epithelial lining and also confirmed the antimicrobial effects of the fibres.

Saxen L, and Asikainen S\textsuperscript{32}(1993), reported suppression of Actinomycetemitans in patients by mechanical debridement plus metronidazole 200 mg t.i.d. for 10 days. The hydroxyl metabolites of metronidazole reported to be responsible for this suppression. Thus concluded that systemic metronidazole therapy would result in marked reduction of anaerobes in the periodontal pockets.

Steenbergh V and Bercy P\textsuperscript{33} (1993), evaluated the efficacy of subgingivally applied 2\% minocycline ointment in 103 patients with periodontitis. Results showed that drug treated patients show significant reduction in pocket depth when compared to control sites.

Stoltze K and Michale S\textsuperscript{34} (1992), treated 14 patients with periodontal pockets with 25\% metronidazole dental gel. The results indicated that high concentration of metronidazole could be obtained in periodontal pockets without inducing plasma concentrations.

Stoltze K Michale S\textsuperscript{35} (1992), treated 12 patients with one applications of 25\% metronidazole gel. Gingival crevicular fluid (GCF) was collected at 4,8,12, 24 and 36 hours after application and analyzed for drug content. The results shown that GCF concentration was maintained about MIC in 92\% of patients at 12\textsuperscript{th} hour, only 8\% of the patients retained the drug in GCF at 36 hours.