Dental implants of tinidazole were formulated using Poly (ε-caprolactone), a biodegradable polymer and evaluated. Clinical evaluation was carried out to evaluate the usefulness in periodontal therapy. Gingival crevicular fluid concentration of the drug was found to be 4.9±13.2 μg 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 commensal flora of the oral cavity and may also pose a risk of overgrowth 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.

The recognition that destructive periodontal diseases may be caused by specific microorganisms in periodontal pockets has led to an increased interest in and usage of antibacterial agents in periodontal therapy. Local chemotherapy by sustained delivery systems has been recently developed which may prolong the effect. However these devices suffer a major disadvantage that the polymer strip must be removed from the periodontal pocket after the release of the agent has been completed and might also cause local mechanical irritation and disturb periodontal repair. To overcome these disadvantages, a biodegradable sustained release dental implants containing tinidazole were developed. The drug concentration in gingival crevicular fluid (GCF) was determined to evaluate the usefulness of the dental implant in periodontal chemotherapy.

Poly (ε-caprolactone) (mol wt 35,000) was obtained from Polyscience Inc, Warrington, PA and Carbopol (974P NF) was obtained from Aldrich Chemical Company, Milwaukee, Wisconsin, USA. Tinidazole was a gift sample from Cheminor labs. Hyderabad. Dichloromethane was purchased from E. Merck Ltd. Mumbai.

Dental implants containing tinidazole were prepared as follows. Poly (ε-caprolactone) (900 mg) was dissolved in 5 ml of dichloromethane. Tinidazole (60 mg) and Carbopol (180 mg) were then dispersed uniformly by using sonicator. The resultant viscous mass was poured on to a glass mould of 5x3 cm size lined with aluminium foil. The solvent was evaporated at room temperature. The dried film was then cut into 0.5x0.5 cm size. Each film contained 1 mg of the drug. The drug, carbopol and polymer ratio was 1:3:15, respectively.

Ten patients who visited College of Dental Surgery, Kasturba Hospital, Manipal, without any systemic disorder and with deep periodontal pockets were selected after obtaining informed consent. Patients received the implants containing tinidazole into periodontal pockets and retained without any sutures and surgical dressings. Since carbopol was used in the formulation, which swells in the aqueous environment and adhere to mucosa thereby making the use of mechanical retention aids or periodontal packs to support the implant in the periodontal pocket unnecessary, GCF and saliva were collected at the baseline (before placing
the implant) then at every hour for the next 8 h and at every recall visit (on 1, 2, 10, 20, 30 and 40 d).

The experimental tooth surface was gently cleaned with sterile gauge to remove saliva and other debris. A filter paper disc of 6 mm diameter was placed into the periodontal pocket in such a way that at least 2 mm of the paper disc was inside the gingival sulcus or periodontal pocket. It was left in position for 3 min, after which it was removed and immediately transferred into a vial containing isotonic phosphate buffer of pH 7.2. To collect the salivary samples two filter paper discs were placed on the floor of the mouth for 3 min and then transferred into the vials.

The maximum amount, 3 mg of GCF or saliva was found to be absorbed by the filter paper disc after 3 min. The vials containing the samples were then closed and vigorously shaken for 2 min and filtered. The absorbance of the filtered solution was measured at 316 nm using a Shimadzu UV/Vis Spectrophotometer. The GCF and saliva collected at baseline served as the control sample. Drug concentration per mg of GCF and saliva was then computed.

Fig. 1 shows drug concentration in GCF and saliva during the time after insertion of the implant, drug was detected in all samples taken after '0' time. The drug concentration reached its maximum 4.9±3.2 μg per mg of GCF at 3 h, thereafter decreased and maintained at 1.85 μg/mg of GCF throughout the 40 d of the study. The amount of the drug in saliva was 0.81±0.52 μg/mg of saliva with $t_{max}$ of 1 h.

For the chemotherapy of periodontal diseases an effective concentration of the chemotherapeutic agent in the periodontal tissues and hence in gingival crevicular fluid must be maintained for an adequate duration of time to inhibit the growth of various periodontopathic organisms8.

Therefore, in the present study, the drug concentration in GCF was estimated to clarify whether the effective concentrations are reached in periodontal pocket for the required duration of time. Salivary flow rate is a principal factor controlling the removal of all agents applied topically to the oral mucosa including the periodontal pockets. Retention of the drugs in the oral cavity depends on both salivary flow rate as well as GCF release of the drug from the polymer matrix in case very high concentration of drugs flow out of the periodontal pocket. There are chances that a very high concentration of drugs may be retained in the saliva which might suppress the normal commensal flora of the oral cavity and may also pose a risk of over growth of opportunistic organisms causing several adverse effects. Therefore, in the present study salivary drug concentration was determined and found that low drug concentration through out the period of study which is desirable. It was also reported that tinidazole inhibits almost all strains of Actinobacillus actinomycetemcomitans, Bacteroides intermedius, Capnocytophaga and Eikenella Corrodenus (about 69 strains) at levels of less than 0.28-1 μg/ml10,11.

Thus the present study clearly demonstrated that the dental implants developed were capable of releasing tinidazole and maintain its concentration well above MIC for many periodontal pathogens in GCF for about 40 d. Therefore, tinidazole dental implants formulated in Poly (ε-caprolactone), a biodegradable polymer may be novel and ideal drug delivery system in future for the effective treatment of periodontitis.

REFERENCES
5. Deasy, P.B., Collins, A.E.M., MacCarthy, D.J. and Russell, R.J.,

Fig. 1: Tinidazole concentration profiles in GCF and Saliva.

Tinidazole concentration profile in GCF (- - -) and saliva (- - -) from biodegradable dental implants after insertion into the periodontal pocket of the patients with perodontitis.
The present study has three primary objectives. Firstly, in view of the low aqueous solubility of celecoxib, solid dispersions of the drug were prepared and evaluated. Different carriers were chosen and a constant drug to carrier ratio was maintained. The solid dispersions obtained were subjected to solubility and dissolution studies including dissolution rate and efficiency. The best carrier was polyvinylpyrrolidone-vinyl acetate co-polymer, as it increased the solubility by a factor of ten. It also exhibited marked increase in the dissolution rate and efficiency. Secondly, the effect of the surfactant sodium lauryl sulphate on the dissolution rate of celecoxib was investigated. The solubility of a poorly soluble drug is one of the most important factors influencing its dissolution rate and bioavailability. Presence of a surfactant in the dissolution medium permits an experimental situation similar to in vivo conditions and hence results in meaningful in-vitro observations. Dissolution study was conducted using various concentrations of sodium lauryl sulphate employing USP dissolution rate testing apparatus 1. Ultimately, a dissolution medium, which gave reproducible results in vitro was designed. Finally, possible drug excipient interactions between celecoxib and the commonly used excipients including those used in the preparation of its solid dispersions were investigated by storing their respective mixtures at various temperatures and humidity conditions followed by evaluating them with reference to physical and chemical stability and the results were confirmed by IR and DSC spectral studies. Polyvinylpyrrolidone was found to be the most satisfactory excipient. Degradation was evident with all other excipients studied although only at elevated temperatures.

Celecoxib is a NSAID, which exhibits potent antiinflammatory and analgesic action by inhibiting prostaglandin synthesis by specifically inhibiting COX-2 enzyme. It is practically insoluble in water and aqueous fluids and because of this; its oral bioavailability is dissolution rate limited. In addition, very low values for the dissolution of the drug were obtained in in vitro dissolution studies using buffer pH 1.2 as dissolution media. To overcome the above problems and to improve its aqueous solubility, solid dispersions of the drug were prepared and evaluated. To obtain an experimental condition similar to in vivo (i.e., taking into consideration the bile acids present in the stomach) sodium lauryl sulphate was included in the dissolution media and the effect

---

*For correspondence
E-mail: kusumal62@yahoo.com