RESEARCH ARTICLE

Clinical studies and antimicrobial activity of ciprofloxacin hydrochloride medicated dental gels for periodontal infection

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For the effective treatment of periodontitis, ciprofloxacin hydrochloride (HCl) medicated dental gels are prepared with different hydrophilic polymers (MC, HPMC, HPC, and HEC) in different concentrations of propylene glycol. The formulations are subjected to various physicochemical studies like pH, spreadability, extrudability, viscosity, drug content, *in vitro* drug release, and rheological and stability studies. During the rheological studies plots of shear rate versus viscosity showed that all the gels were non-Newtonian and exhibited pseudoplastic behavior. *in vitro* drug release studies were carried out in the diffusion cell using a pH 7.2 phosphate buffer as a receptor medium. Formulations exhibited an extended release of the drug for over a period of 6 hours and the release depended on the type of polymer and concentrations of propylene glycol used. Stability studies showed no significant variations ($P > 0.05$) in pH, spreadability, viscosity, extrudability, and drug content. An *in vitro* release study concluded that hydrocolloid based ciprofloxacin hydrochloride medicated dental gels appear to be probably extend the release of ciprofloxacin hydrochloride. Optimal formulations were selected for *in vivo* or clinical studies. The clinical evaluation of ciprofloxacin hydrochloride gels was carried out to determine the efficacy in the treatment of periodontitis. Six groups, each containing five patients, were used in the study. All the patients were evaluated for plaque index (PI) and gingival index (GI), probing depth (PD), and bleeding on probing (BOP). In all these studies, two groups were treated with formulations alone and another two groups were treated with formulations along with scaling and root planning. One group was treated with scaling and root planning only, whereas, the last group was treated as control (No treatment). All the groups showed a similar baseline PI. However, the PI values decreased remarkably in the groups treated with formulation along with scaling and root planning when compared to the other groups. Similarly, the results of GI, BOP, and PD also showed a significant reduction ($P < 0.05$) in the groups treated with formulation along with scaling and root planning compared to other groups. The above studies revealed that the adjunctive use of ciprofloxacin hydrochloride gels along with scaling and root planning results in significant benefits, in the treatment of periodontitis.

Key words: *Antimicrobial activity, bleeding on probing, clinical trials, gingival index, plaque index, probing depth*

INTRODUCTION

Pharmaceutical technologists today are able to provide drug delivery systems with very precise control over drug release for a prolonged period of time, eliminating the need for frequent dosing and minimizing side effects, thereby increasing patient compliance and comfort. Dental diseases are among the most widespread chronic disorders affecting mankind. The high incidence of caries and periodontal diseases is borne out by epidemiological studies carried out in many parts of the world. Periodontitis, the severely debilitating disease of the periodontium, is characterized by the loss of bone and collagen support of the affected teeth. The term "Periodontitis" collectively represents several diseases, but with common causative organisms. *Actinobacillus actinomycetemcomitans* is a pathogen responsible for juvenile periodontitis, while *Bacteroides gingivalis and B. melaninogenicus* are the subspecies. *Prophyromonas gingivalis, Prevotella intermedia, and Staphylococci subspecies epidermidis and aureus* are responsible for adult periodontal disease.[1]

Periodontal disease is a major problem among the diseases of the oral cavity. Periodontal disease, if not

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treated, results in the destruction of the bone and soft tissue supporting the tooth leading to tooth loss. The treatment of periodontitis is directed at slowing down or arresting the progression of the disease by regenerating the alveolar bone, periodontal ligaments, and root cementum and preventing recurrence of the disease.

In the early stage of periodontitis, scaling and root planning is usually effective in removing calculus and plaque, thereby, reducing bacterial count and probing depth. As the probing depth increases, the effectiveness of scaling and root planning decreases. Therefore, in recent years, many antibiotics are either topically or systematically used in the treatment. Systemic antibiotic therapy has certain advantages. However, long-term use of systemic antibiotics is associated with several side effects such as development of resistance, hypersensitivity, and unwanted side effects.

Site-specific therapy has three potential advantages: Decreased drug doses, increased drug concentration at the site of infection, and reduced systemic side effects such as gastrointestinal distress.[2] Periodontal disease treatment[3,4] with a localized drug delivery system aims at delivering a therapeutic agent at a sufficient level inside the periodontal pocket and at the same time minimizes the side effects associated with systemic drug administration. Hence, drug delivery systems containing antimicrobial agents are used for delivery to the periodontal pocket. The use of a topical antimicrobial agent for treatment of periodontitis is generally preferred as it allows direct access of high local concentration of antimicrobial agents. Many antimicrobial agents have been tried as mouth rinses in the treatment of periodontal diseases, with poor-to-moderate degrees of success. Tetracycline irrigation has been found to be effective in the control of periodontal disease. The effect of irrigation to the periodontal pocket with control and scaling-root planning groups has been tried. Clinical and microbiological parameters were monitored and tetracycline irrigation alone or scaling and root planning alone resulted in statically significant improvement in the subgingival micro flora from a diseased to a healthy state.[5]

Over the last decade hydrogels formed from natural, semi-synthetic, and synthetic polymers have been confirmed as vehicles for different types of pharmaceutical applications. They have good viscosity, satisfactory bioadhesivity, and are without irritating or sensitizing actions.[6] Dental gels have been used over the decades, either for cosmetic or therapeutic purposes. Dental gels possess good spreadability and consistency and are therefore accepted by a large population. The object of the present study is to develop ciprofloxacin hydrochloride medicated dental gels for an extended period of time and to study the effect of various mucoadhesive polymers on the *in vitro* characteristics of gels. The clinical evaluation of ciprofloxacin hydrochloride was carried out to determine the efficacy in the treatment of periodontitis. The ethical committee of the Navodaya Medical College, Raichur, approved the clinical trial protocol. The clinical evaluation was carried out under the direct supervision of a dentist. The study was explained orally and in writing to all the subjects who participated in the study. In the present study the number of groups selected were five and the number of subjects in each group was six. The age of the patients was between 21 and 55 years. The patients were with localized periodontal pockets measuring 6-10 mm, which bled on probing at the initial visit. Patients were free to withdraw or could be withdrawn from the study at any time. The following information of a patient was recorded in the standard format prepared for the study under direct supervision of a dentist: Name, age, sex, gingival index, plaque index, probing depth (mm), and bleeding on probing.

MATERIALS AND METHODS

Ciprofloxacin HCl and aspartame were procured as a gift sample from Aan Pharma Pvt Ltd., Rakanpur, Gujarat. Glycerin, methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), and propylene glycol (PG) purchased from S.D.Fine Chem. Ltd., Mumbai. Hydroxypropyl cellulose was procured as a gift sample from Cipla Laboratories Bangalore. Kaolin purchased from CDH. Pvt. Ltd. New Delhi, Mueller Hinton broth from Himedia Laboratories Ltd., Mumbai, India, and methyl paraben from Genuine Chemicals Co., Mumbai. Empty aluminum collapsible tubes were purchased from Digvijay containers and closures, Mumbai. All other reagents were of analytical grade.

Methods

Formulation of medicated gels

Gels were prepared by dispersing the polymer at different concentrations in water by continuous stirring for a period of 2 hours. The drug was dissolved in propylene glycol and the solution was added gently to the above polymer dispersion, under continuous stirring. The mixture was stirred gently until a homogeneous gel was formed. The gels prepared were stored in wide mouthed bottles. Entrapped air bubbles were removed by keeping the gels in a vacuum oven for 2 hours. All the samples were allowed to equilibrate at least for 120 hours at room temperature, prior to performing rheological measurements. The compositions of the various gels are shown in Table 1.

Evaluation of ciprofloxacin HCl medicated gels

Prepared gels were evaluated for drug content analysis, pH, viscosity, spreadability, and tube extrudability. In drug content analysis[7] a specified quantity (1.0 gm) of medicated dental gel was taken and dissolved in pH 7.2 phosphate buffer. The solution was filtered through Whatman filter paper (0.45 μ). The absorbance of the solution was measured using a UV spectrophotometer (SHIMADZU, UV- 1700, Japan) at λ 276 nm against blank. The measurement of pH was done by using a digital type pH meter (Digison digital pH meter 7007, Mumbai), by dipping the electrode completely into the gel so as to cover the electrode. The viscosity measurements of the gels were

Table 1: Composition of ciprofloxacin HCl medicated dental gels (%w/w)

Ingradients (% w/w)	CG1	CG2	CG3	CG4	CG5	CG6	CG7	CG8	CG9	CG10	CG11	CG12
Ciprofloxacin HCl	1	1	1	1	1	1	1	1	1	1	1	
MC	5	5	5	-	-	-	-	-	-	-	-	-
HPMC K4M	-	-	-	2.5	2.5	2.5	-	-	-	-	-	-
HEC	-	-	-	-	-	-	3	3	3	-	-	-
HPC	-	-	-	-	-	-	-	-	-	6.5	6.5	6.5
Aspartame	0.20	0.20	0.20	0.20	0.20	0.20	020	0.20	0.20	0.20	0.20	0.02
Propylene glycol	0	10	20	0	10	20	0	0	20	0	10	20
Methyl paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Propyl paraben	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.2
Purified water	100	100	100	100	100	100	100	100	100	100	100	100

HPMC = Hydroxypropyl methylcellulose K4M; HEC = Hydroxyethyl cellulose; HPC = Hydroxypropyl cellulose; MC= Methyl cellulose

evaluated using a Brookfield digital viscometer (DV - III Ultras programmable Rheometer, USA) by applying increasing values of the shear rate, in order to reveal a possible flow behavior of the pastes. All viscosity measurements were performed at a controlled temperature of 30 ± 2°C. The spreadability[8] was measured by about 1 gm of medicated gel, which was weighed and kept at the center of the glass plate (10 × 10 cm) and another glass plate was placed over it carefully. A two kilogram weight was placed at the center of the plate and care was taken to avoid sliding of the plate. After 30 min the diameter of the gel in centimeters was measured. Tube extrudability[9] was then determined by measuring the amount of gel that had extruded through the tip when a pressure was applied on the gel-filled tubes. The formulation under study was filled in a tube with a nasal tip of 5 mm opening.

In vitro drug release studies from various medicated gels was measured through standard cellophane membrane using a modified Keishery-Chien diffusion cell. Prior to the study, a cellophane membrane was soaked in diffusion medium for 4 hours, and then placed on the support screen of the diffusion cell assembly. All the joints were properly sealed with an adhesive tape to avoid penetration of the diffusion medium. Phosphate buffer pH 7.2 was used as the receptor medium and 1 g of the gel was placed on the donor side. The receptor medium was kept at 37 ± 1°C. At predetermined time intervals, 5 ml of the samples were withdrawn from the receptor compartment and replaced with the same volume of phosphate buffer pH 7.2. Absorbance of the solutions was measured at λ 276 nm.

Characterization of ciprofloxacin HCl medicated gels

Stability studies

The stability studies were carried out (ICH guidelines) for optimum formulations at different temperature conditions 25 ± 2°C, 37 ± 2°C, and 4°C at humidity (75 ± 5% RH) for 3 months, in stability chambers, and spreadability, tube extrudability, pH, and drug content were studied.

Microbiological studies

In case of gels, the release of the drug from the matrix would have an impact on the efficacy of the gel's preparation and hence its effect on sensitive organisms was analyzed, to establish the efficacy of the gel's preparation in terms of antimicrobial activity.

The given samples of ciprofloxacin hydrochloride formulations were dissolved in sterile distilled water to get a final concentration of 5 mcg/ml. Pure drug samples were also dissolved in sterile distilled water to get a concentration of 5 mcg/ml.

Minimum inhibitory concentrations[10]

Mueller Hinton broth was prepared by dissolving 2.1 g of Mueller Hinton broth (Himedia Laboratories Ltd., Mumbai, India) in 100 ml distilled water followed by sterilization. Antibiotic solution of 5 mcg/ml (2 ml) was added to the first tube containing 2 ml of double strength Muller Hinton broth (2.1 g in 50 ml) to get a concentration of 2.5 mcg/ml. Serial dilutions were made to get concentrations of 1.25, 0.625, 0.3125, 0.1562, 0.0781, and 0.0390 mcg/ml in Mueller Hinton broth. One tube containing the medium alone, with the organism, was kept as a positive control. Another uninoculated medium was kept as a negative control. Experiments were performed for ciprofloxacin formulations using sensitive organisms to establish the efficacy of the preparations, in terms of antimicrobial activity (against *E. coli, Staphylococcus aureus, Pseudomonas aeruginosa, and Bacillus subtilis* microorganisms).

Clinical studies of ciprofloxacin HCl medicated

Study design

All test teeth were required to have a pocket with probing depths between 6-10 mm with bleeding on probing. A minimum of 14 days before baseline, all patients were evaluated for probing depth (PD), bleeding on probing (BOG), plaque index (PI), and gingival index. All patients received oral hygiene instructions and full mouth supra gingival and sublingual scaling, root planning, and polishing. Those patients having a pocket depth 5 mm or more were selected for the final study. Before initiating the treatment, the gingival health status of the selected teeth was determined clinically according to the gingival index.[10] The plaque index of the selected teeth was determined using the plaque index[11] at baseline. Each patient was examined clinically and all patients

in the study received a full mouth supra gingival, subgingival scaling and polishing one week before the experiment. Each patient received only one treatment in this parallel design study. The following treatments were initiated at the baseline appointment. All patients were informed to follow oral hygiene instructions.

Group 1: CG-11 (Ciprofloxacin HCl gel-11), Group 2: CG-5 (Ciprofloxacin HCl gel-5), Group 3: CG-11 + Scaling with root planning, Group 4: CG-5 + Scaling with root planning, Group 5: Scaling with root planning, Group 6: Control (No treatment). The formulations were administered twice daily, in the morning: after breakfast, at night, and before sleeping, for 30 days, at the affected site, by using a needleless syringe. The semisolid mass was completely and safely inserted into the pocket using a blunt stainless steel needle.

Clinical measurements

PI[12] was used to evaluate the level of plaque control throughout the study. Scoring was done on the entire dentition or on selected teeth. The surfaces examined were the four gingival areas of the tooth. Scoring was done at screening, baseline, and on the fifteenth and thritieth days during treatment. Scores for the plaque index that ranged from 0-3. 0 were excellent, 0.1-0.9 were good, 1.0-1.9 were fair, and 2.0-3.0 were poor. GI was the severity of gingivitis, and was scored on selected teeth. The tooth surface was divided into four areas, that is, distofacial, facial, mesiofacial, and lingual/palatal. Criteria for GI[13] were 0.1-1.0 was mild gingivitis, 1.1-2.0 moderate gingivitis, and 2.1-3.0 severe gingivitis. BOP was recorded as present or absent at the time of conventional probing at each site. These were expressed as bleeding sites (%). PD was measured by a reference point, and was made on the tooth surface by placing a piece of radiographic film with glass ionomer cement. The PD was measured as the distance from the free gingival margin to the base of the periodontal pocket. Measurements were taken at the screening, baseline, and on the fifteenth and thirtieth days of the treatment, to monitor disease stability. The results were analyzed by two tailed Student's *t*-test using Graph Pad Instat Software (1.13 version) and $P < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

The drug content of different ciprofloxacin HCl gels is shown in Table 2. The drug content was found to be in the range of 96.30-99.24%, with a small standard deviation (≤0.52%), suggesting that the drug was uniformly distributed in the gels. Plots of shear rate versus shear stress are shown in Figure 1 for MC, HPMC, HEC, and HPC gels. All the formulations showed non-Newtonian flow and exhibited pseudoplastic behavior, suggesting that the gels do not flow at low shear stress and room temperature. The viscosity of the ciprofloxacin HCl gels increased as the concentration of propylene glycol increased. Spreadability values of ciprofloxacin HCl gels are shown in Table 2. The spreadability was found to be in the range of 6.6-7.5 cm. Spreadability of the ciprofloxacin HCl gels was not much influenced by the type of hydrocolloids. However, spreadability values of the gels decreased as the concentration of the propylene glycol increased in the formulations. The

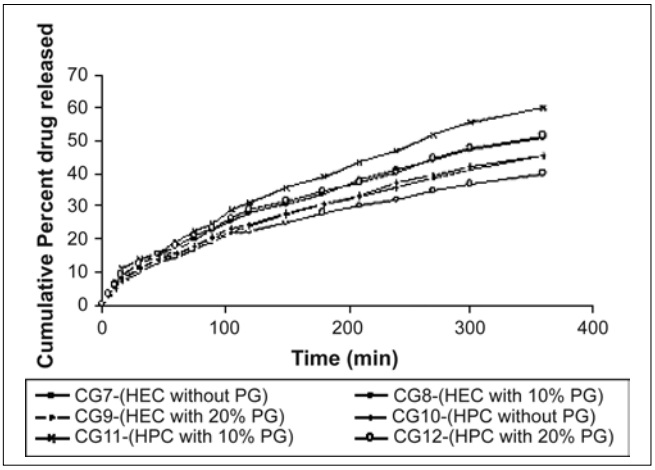

Figure 1: Rheological studies of ciprofloxacin hydrochloride gels. Effect of concentrations of propylene glycol on the release profiles of ciprofloxacin hydrochloride gels containing MC and HPMC. Effect of concentrations of propylene glycol on the release profiles of ciprofloxacin hydrochloride gels containing HEC and HPC

Table 2: Physical parameters of ciprofloxacin HCl gels

Formulation	Drug content (%) ± SD, n = 3	Viscosity (cps)	Spreadability (cm) ± SD, n = 3	Tube extrudability (%) ± SD, n = 3	pH ± SD, n = 3
CG1	97.86 ± 0.30	45125.63	7.1 ± 0.06	95.33 ± 1.15	6.12 ± 0.02
CG2	97.34 ± 0.30	46514.58	7.0 ± 0.12	91.67 ± 1.53	6.10 ± 0.01
CG3	96.99 ± 0.52	46658.32	6.7 ± 0.10	93.33 ± 1.53	6.23 ± 0.02
CG4	96.30 ± 0.03	45786.56	7.1 ± 0.10	94.33 ± 0.58	6.25 ± 0.02
CG5	98.03 ± 0.52	46886.88	6.9 ± 0.15	92.00 ± 1.00	6.05 ± 0.02
CG6	99.24 ± 0.30	46998.97	6.8 ± 0.15	91.67 ± 1.53	6.15 ± 0.02
CG7	97.51 ± 0.52	42113.78	7.5 ± 0.10	94.00 ± 1.00	6.06 ± 0.04
CG8	96.82 ± 0.30	42458.69	7.1 ± 0.20	94.67 ± 1.15	6.21 ± 0.02
CG9	98.20 ± 0.30	42856.47	6.9 ± 0.15	93.00 ± 1.00	6.17 ± 0.02
CG10	98.03 ± 0.52	45623.54	7.1 ± 0.10	91.67 ± 1.53	6.25 ± 0.01
CG11	99.24 ± 0.30	45733.65	6.9 ± 0.15	90.33 ± 1.15	6.24 ± 0.02
CG12	99.07 ± 0.52	45821.69	6.6 ± 0.10	90.33 ± 1.53	6.23 ± 0.03

decrease in spreadability was relative to that of changes in the viscosity of the gels. Tube extrudability values of ciprofloxacin HCl gels are shown in Table 2. For various formulations, tube extrudability was found to be in the range of 90.33-95.33%. Tube extrudability of the ciprofloxacin HCl gels was also not influenced by the type of hydrocolloid. However, tube extrudability values of the gels decreased as the concentration of the propylene glycol increased in the formulations. The decrease in the tube extrudability values was relative to the changes in the viscosity of the gels.

The results of the *in vitro* drug release study reveal that *in vivo* release can also help in the development of new drug formulations. The influence of different hydrocolloids on the release of ciprofloxacin HCl from different gels through the standard cellophane membrane was examined. The release profiles are compiled in Figures 2 and 3, and the amount of drugs released at 360 minutes are presented in Table 3. The release of ciprofloxacin HCl from different hydrocolloid containing gels was found to be slower. One of the approaches to improve the topical drug delivery was to use the co-solvents as enhancers. In this connection, numerous compounds were evaluated. Among them, propylene glycol was the most commonly used co-solvent in topically applied dosage forms. In this study, the effect of the concentration of propylene glycol (10 and 20% v/v) on the release of ciprofloxacin HCl has been studied. The release of the drug increased as propylene glycol was incorporated, and the drug release rate from these hydrocolloid gels also varied depending on the concentration of propylene glycol in the formulations. The flux values were found to be increased [Table 3], suggesting that the release of ciprofloxacin HCl increased with the addition of propylene glycol (10%). It was believed that increasing the concentration of an active compound (ciprofloxacin HCl) within the co-solvent (propylene glycol) could give rise to persistent solvated complexes, due to a higher release of the drug. In general, it is believed that an increase in the concentration of propylene glycol in gels generally increases permeation of the drug. However, the flux value decreased, as the concentration of propylene glycol increased from 10 to 20% (CG3, CG6, CG9, and CG12). Analogous results, that is, lower release rates with higher concentrations of propylene glycol were reported.[14,15] The decrease in release could be attributed to the higher solubility and affinity of ciprofloxacin HCl in the vehicle. These results show the action of propylene glycol as a co-solvent, since, flux declines as the affinity of the drug to the vehicle rises.[14,15] Therefore, Lippold[16] recommended the use of suspensions in order to optimize the thermodynamic activity of the drug in its vehicle to achieve maximum flux. Thus in the present study, higher fluxes were noticed with formulations containing modest amount (i.e. 10%) of Propylene glycol indicating that the drug was in more suspended state. In addition, the addition of propylene glycol and/or increase in the concentration of the propylene glycol increased the bulk viscosity of the gels. However, the flux (and drug release) values [Table 2] increased. This apparent lack of correlation between bulk viscosities of the gels and the flux (and drug release) values indicate that bulk viscosity is not the primary factor[17,18] that affects the release of the drug from the vehicle.

When the release data were fit in different kinetic models, high correlation coefficients ($R^2 > 0.9672$) were obtained in first-order models compared to zero order kinetics ($R^2 < 0.8797$), suggesting that release of drugs from gels followed first-order kinetics. Higuchi correlation coefficients ($R^2 > 0.9903$) obtained with the Higuchi model indicated that release of the drug from ciprofloxacin HCl gels was compliant with the Higuchi diffusion model. The results are compiled in Table 3.

Stability studies of gels at lower (4 ± 2°C), room (25 ± 2°C), and elevated (37 ± 2°C) temperatures (humidity 75 ± 5% RH) did not show any significant ($p < 0.05$) changes in the spreadability, tube extrudability (%), pH, or drug content of the gels, compared to those before stability studies. The data is given in Table 4.

In the prepared gel formulations, the antimicrobial activity inference in different organisms was as per the data given in Table 5. All organisms showed that the results of antimicrobial activity in the prepared formulations (gel) showed less activity

Table 3: *In vitro* release parameters of different ciprofloxacin HCl gels

Formulation	Flux *Jss* mg/cm²/h (±SD, n = 3)	% Drug released in 360 min (±SD, n = 3)	Zero order kinetic R^2	1st order kinetic R^2	Higuchi model R^2
CG1	0.182 ± 0.003	43.87 ± 0.029	0.8412	0.9776	0.9962
CG2	0.216 ± 0.006	54.70 ± 0.029	0.8021	0.9835	0.9965
CG3	0.216 ± 0.006	49.00 ± 0.029	0.8516	0.9859	0.9938
CG4	0.214 ± 0.007	50.07 ± 0.023	0.8330	0.9922	0.9960
CG5	0.286 ± 0.007	67.77 ± 0.029	0.7981	0.9921	0.9945
CG6	0.250 ± 0.003	57.32 ± 0.029	0.8503	0.9911	0.9918
CG7	0.148 ± 0.007	40.11 ± 0.023	0.8154	0.9672	0.9978
CG8	0.212 ± 0.003	51.01 ± 0.023	0.8516	0.9840	0.9946
CG9	0.198 ± 0.006	45.35 ± 0.023	0.8581	0.9821	0.9950
CG10	0.184 ± 0.003	45.67 ± 0.029	0.8450	0.9816	0.9954
CG11	0.258 ± 0.006	60.07 ± 0.029	0.8797	0.9936	0.9903
CG12	0.212 ± 0.009	51.38 ± 0.029	0.8390	0.9822	0.9956

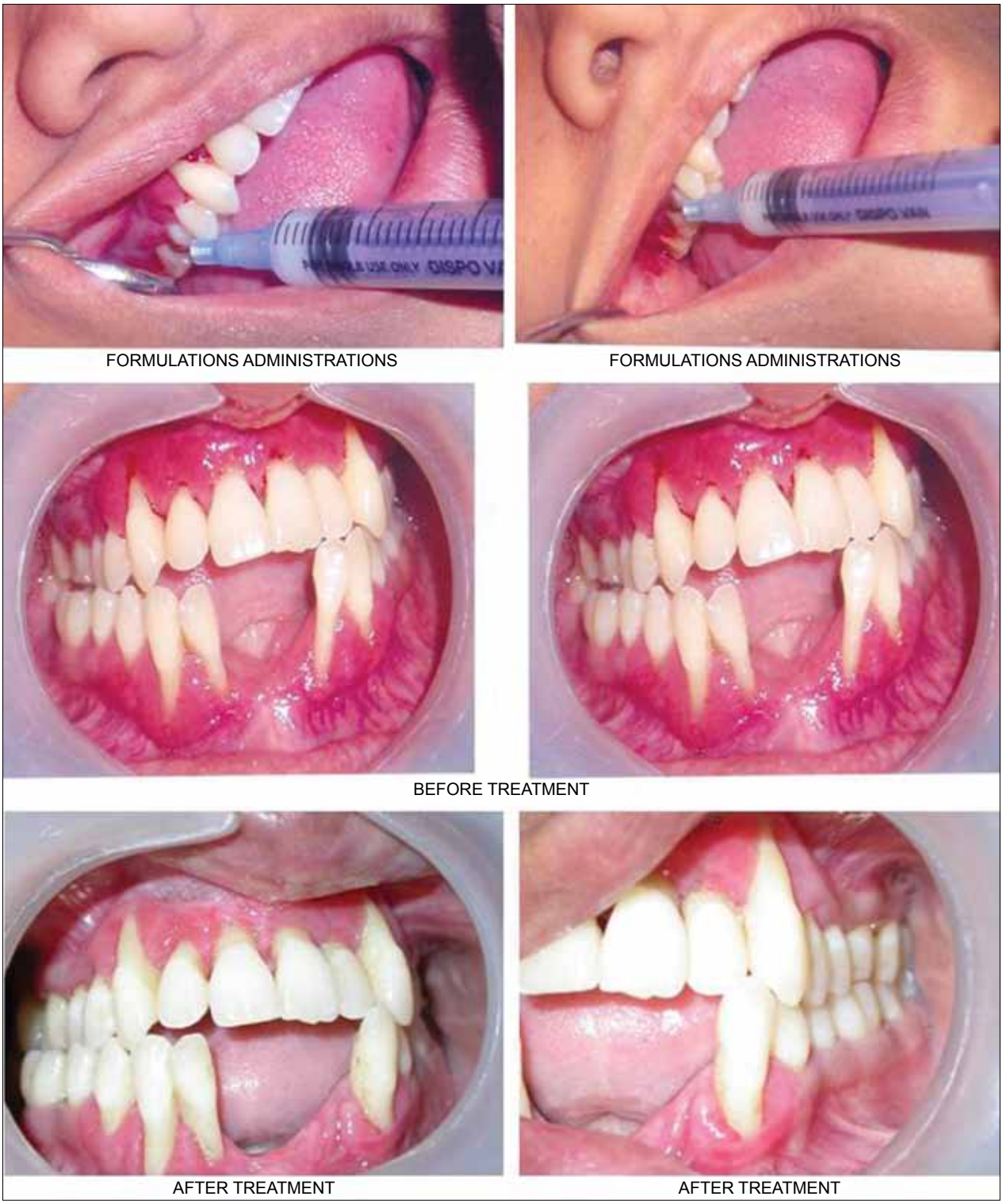

Figure 2: Photographs showing the effects of treatment during the clinical study (Case - 1)

when compared to that in the pure drug. In *E. coli* the formulation showed growth from 0.1562 mcg/ml concentrations, whereas, pure drugs showed growth from 0.0781 mcg/ml. In case of *Pseudomonas aeruginosa* the formulation showed growth from 0.1562 mcg/ml concentrations, whereas, the pure drug showed growth from 0.0781 mcg/ml. In *Bacillus subtilis* the formulation showed growth from 0.1562 mcg/ml concentrations, whereas, the pure drug showed growth from 0.0781mcg/ml. *Staphylococcus aureus* showed the results of the antimicrobial activity of ciprofloxacin hydrochloride gel. The

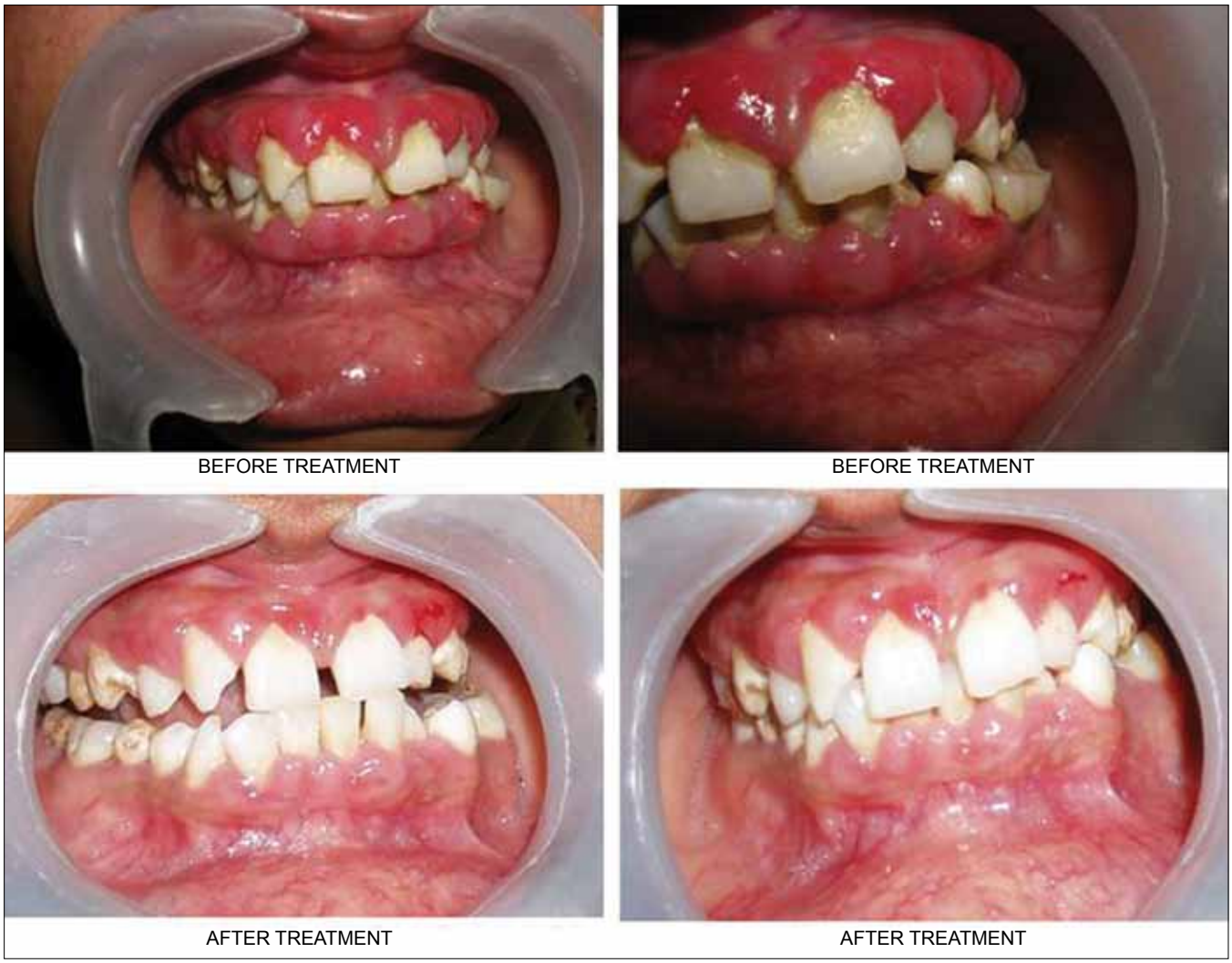

Figure 3: Photographs showing the effects of treatment during the clinical study (Case - 2)

prepared formulation (gel) showed less activity when compared to the pure drug. The prepared formulation showed growth from 0.1562 mcg/ml concentration and the pure drug showed growth from 0.0781 mcg/ml.

The *in vivo* studies would be the final parameters to ensure that the biological activity of the therapeutic agent is retained in the delivery system. The clinical efficacy of the prepared dental gels of ciprofloxacin HCl was assessed in patients with periodontal pockets.

The results of average plaque scores before and after treatment are presented in Table 6. The results indicated that there was no significant change in the plaque index among different treatment groups, throughout the study, when compared with their respective baseline values. The CG-11, CG-5, and S with P groups showed almost equal reduction in PI. However, CG-11+S with P and CG-5+S with P showed marked reduction in PI, which could be due to the combined effect of the drug and scaling with root planning. The results of the average gingival index before and after treatment are shown in Table 7. The GI values decreased in all the treated groups. The decrease was significantly more from the baseline when compared with the values of the respective groups on the fifteenth and thirtieth days. Drug formulation treatment associated with scaling with root planning showed a high decrease compared to other groups. This could be due to the collective effect of drug and scaling and root planning. The results of BOP are given in Table 8. The results indicated that a highly significant reduction in bleeding was observed with all the treatments. All treatments were effective in reducing the number of periodontal sites. However, drug treatment in association with scaling and root planning showed a complete elimination of bleeding sites at the end of 30 days. The results of PD during the clinical study are presented in Table 9. There was no significant difference between groups at the time of initiation of therapy. A highly significant reduction in probing depth was observed on the fifteenth and thirtieth days, in all the treated groups. During clinical studies, the treated

Table 4: Stability studies data of ciprofloxacin HCl gels

Formulation	Storage temperature	Time of analysis days	Spreadability (cm)	Tube extrudability (%)	pH	Drug content (%)
CG2	4 ± 2°C	30	7.0	92	6.10	97.51
		60	6.8	91	6.08	97.51
		90	6.7	90	6.14	96.99
	25 ± 2°C	30	7.0	92	6.10	97.51
		60	6.9	92	6.09	96.99
		90	6.9	92	6.13	96.99
	37 ± 2°C	30	7.0	92	6.10	97.51
		60	7.1	93	6.12	97.51
		90	7.2	94	6.08	96.99
CG5	4 ± 2°C	30	7.1	94	6.25	96.47
		60	6.9	93	6.24	96.47
		90	6.8	91	6.23	95.55
	25 ± 2°C	30	7.1	94	6.25	96.47
		60	7.1	92	6.22	95.55
		90	7.0	92	6.24	95.55
	37 ± 2°C	30	7.1	92	6.25	96.47
		60	7.0	93	6.22	96.47
		90	6.9	94	6.24	95.55
CG6	4 ± 2°C	30	6.9	92	6.05	98.55
		60	6.8	91	6.10	98.55
		90	6.7	89	6.09	98.03
	25 ± 2°C	30	6.9	92	6.05	98.55
		60	6.8	90	6.10	98.03
		90	6.9	91	6.08	98.03
	37 ± 2°C	30	6.9	92	6.05	98.55
		60	6.9	93	6.12	98.55
		90	7.0	94	6.14	98.03
CG11	4 ± 2°C	30	6.8	92	6.15	99.07
		60	6.7	91	6.18	99.07
		90	6.6	90	6.19	98.55
	25 ± 2°C	30	6.8	92	6.15	99.07
		60	6.8	91	6.18	99.07
		90	6.9	90	6.12	98.55
	37 ± 2°C	30	6.8	92	6.15	99.07
		60	6.9	93	6.20	98.55
		90	7.0	94	6.21	99.55

patients photographs are shown in photographs 1 and 2. Mean reduction in probing depth at the end of 30 days was greater in patients who received scaling with root planning in addition to drug treatment.

CONCLUSION

In conclusion, it can be stated that the physicochemical parameters of both medicated pastes and gels were at optimum level. The *in-vitro* drug release from the gels was controlled and dependent on the formulation variables. The stability studies did not indicate any change in the values of physicochemical parameters. Gels possessed marked anti-microbial activity. The clinical studies demonstrated that the formulation was effective in the treatment of periodontitis. The present study is industry-oriented and contributes to dental sciences, as very few dental formulations exist in the market.

The clinical parameters such as, plaque index, gingival index, bleeding on probing, and probing depth were studied during the treatment. The results indicated that scaling and root planning was insufficient to achieve good therapy. The results of all the above parameters showed that good therapeutic outcome could be achieved with local drug delivery of the drug from gels. The effect was further enhanced when the local delivery was added with scaling to remove calculus and subgingival deposits.

In vivo studies concluded that the pooled data from this study was that the adjunctive use of ciprofloxacin HCl gels resulted in a significant clinical benefit at the end of 30 days. The results indicated that scaling and root planning was insufficient to achieve good therapy, although it was one of the effective treatments for adult periodontitis.[19] This may be because as the depth increased to 5 mm or more, scaling and root planning became less effective.[20] For the periodontal pockets of 5 mm or more depth, the adjunctive use of

Table 5: Microbiological studies of prepared formulations (gels)

Concentrations (mcg/ml)	2.5	1.25	0.625	0.3125	0.1562	0.0781	0.0390	0.01953	0.00976
Organisms: *E. coli*									
Pure drug	-	-	-	-	-	+	+	+	+
Ciprofloxacin HCl gel	-	-	-	-	+	+	+	+	+
Organisms: *Pseudomonas aerugenosa*									
Pure drug	-	-	-	-	-	+	+	+	+
Ciprofloxacin HCl gel	-	-	-	-	+	+	+	+	+
Organisms: *Bacillus subtilis*									
Pure drug	-	-	-	-	-	+	+	+	+
Ciprofloxacin HCl gel	-	-	-	-	+	+	+	+	+
Organisms: *Staphylococcus aureus*									
Pure drug	-	-	-	-	-	+	+	+	+
Ciprofloxacin HCl gel	-	-	-	-	+	+	+	+	+

+= Presence of growth, −= Absence of growth

Table 6: PI scores during the clinical study of ciprofloxacin HCl gels

Treatment formulation code	Plaque index		
	Baseline	15 days	30 days
CG-11	1.44 ± 0.44	1.32 ± 0.41*	1.23 ± 0.26*
CG-5	1.41 ± 0.38	1.26 ± 0.43*	1.21 ± 0.32*
CG-11+S-P	1.39 ± 0.42	1.16 ± 0.34*	1.14 ± 0.30*
CG-5+S-P	1.42 ± 0.46	1.10 ± 0.24*	1.06 ± 0.31*
S-P	1.47 ± 0.42	1.32 ± 0.39*	1.24 ± 0.24*
Control	1.44 ± 0.33	1.42 ± 0.29	-

All values are presented as Mean ± SD, n = 6 CG-11=Ciprofloxacin HCl gel-11; CG-5 = Ciprofloxacin HCl gel-5; S-P=Scaling - root planning alone *Significant ($P < 0.05$) when compared to respective baseline values

Table 7: GI values during the clinical study of ciprofloxacin HCl gels

Treatment formulation code	Gingival index		
	Baseline	15 days	30 days
CG-11	1.66 ± 0.40	0.76 ± 0.26*	0.73 ± 0.35*
CG-5	1.65 ± 0.39	0.71 ± 0.21*	0.69 ± 0.26*
CG-11+S-P	1.59 ± 0.40	0.61 ± 0.23*	0.56 ± 0.20*
CG-5+S-P	1.60 ± 0.41	0.60 ± 0.23*	0.54 ± 0.18*
S-P	1.58 ± 0.28	1.20 ± 0.21*	1.19 ± 0.32*
Control	1.57 ± 0.33	1.58 ± 0.39	-

All values are presented as Mean ± SD, n = 6 CG-11=Ciprofloxacin HCl gel-11; CG-5 = Ciprofloxacin HCl gel-5 S-P=Scaling - root planning alone *Significant (P <0.05) when compared to respective baseline values.

Table 8: Bleeding sites (%) values during the clinical study of ciprofloxacin HCl gels

Treatment formulation code	Bleeding sites (%)		
	Baseline	15 days	30 days
CG-11	90.36 ± 4.06	23.38 ± 8.22*	11.87 ± 4.06*
CG-5	90.36 ± 4.06	23.84 ± 8.14*	12.57 ± 4.06*
CG-11+S-P	93.67 ± 5.12	22.56 ± 4.06*	0.00 ± 0.00*
CG-5+S-P	95.87 ± 4.06	22.78 ± 4.06*	0.00 ± 0.00*
S-P	93.33 ± 5.16	31.67 ± 4.08*	32.36 ± 4.06*
Control	91.66 ± 4.08	86.67 ± 8.16	-

All values are presented as Mean ± SD, n = 6 CG-11 = Ciprofloxacin HCl gel-11; CG-5 = Ciprofloxacin HCl gel-5 S-P = Scaling - root planning alone *Significant ($P < 0.05$) when compared to respective baseline values

Table 9: Change in PD of prepared formulations (gels)

Treatment formulation code	Probing depth (mm)		
	Baseline	15 days	30 days
CG-11	6.58 ± 1.36	1.95 ± 0.46*	1.75 ± 0.42*
CG-5	6.58 ± 0.78	1.98 ± 0.54*	1.73 ± 0.51*
CG-11+S-P	6.36 ± 1.10	1.69 ± 0.41*	1.69 ± 0.39*
CG-5+S-P	6.35 ± 1.04	1.77 ± 0.42*	1.64 ± 0.39*
S-P	6.09 ± 1.10	2.30 ± 0.48*	2.10 ± 0.38*
Control	6.12 ± 1.05	6.00 ± 1.12*	-

All values are presented as Mean ± SD, n = 6 CG-11=Ciprofloxacin HCl gel-11; CG-5= Ciprofloxacin HCl gel-5 S-P=Scaling - root planning alone *Significant ($P < 0.05$) when compared to respective baseline values

an antimicrobial agent may be necessary, to enhance the therapeutic effect, which is indicated by the improved clinical outcome in this study. Thus, it can be concluded that the ciprofloxacin HCl gels prepared in this study promise to be the new therapeutic systems for the effective treatment of periodontal disease.

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