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Research Article on Formulation and Evaluation of Periodontal Metronidazole *In-Situ* Gel

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ABSTRACT

Periodontal diseases are one of the common microbial infections in adults. They are of two types gingivitis and periodontitis. Periodontitis is an inflammatory disease of supporting tissue caused by groups of microorganisms. An aggressive form of periodontitis can be localized and is associated with microorganisms, therefore, treatment by antimicrobial agents is most appropriate. The main aim of antibiotic therapy is to establish a concentration of drugs that inhibits pathogenic bacteria. Metronidazole specifically acts on gram-negative anaerobic, Facultative bacteria which are responsible for periodontal disease. Metronidazole requires a very low minimum inhibitory concentration to inhibit the growth of periodontal pathogens. The drug and polymer were characterized for molecular weight, solubility, thermal analysis, UV Spectra analysis, and FTIR analysis. Pluronics are an ABA type of copolymers and showed characteristic property of thermoreversible gelation. By Compatibility study drug was found to be compatible with the formulation excipient. Gelation temperature and pH of all formulations were found to be in the range of respectively. All the formulations except F showed satisfactory syringeability. The viscosity of all prepared formulations was found in the range of 6-7 centipoise. All the formulations were developed using a combination of poloxamer-F-127 and various other excipients like HPMC-K100, Carbopol-934, and Xanthan gum. Formulation F-10 showed satisfactory results for *in-vitro* gelling capacity, rheology, and other physical properties. Based on maximum desirability and cost-effectiveness formulation containing carbopol-934 0.25% was considered as the best-optimized batch.

INTRODUCTION:

Periodontal disease is a collective term described to several pathological conditions characterized by degeneration and inflammation of gums, periodontal ligaments, alveolar bone, and dental cementum. It is a localized inflammatory response caused by bacterial infection of a periodontal pocket associated with subgingival plaque[1,2]. Although bacteria are the primary cause of periodontal disease, the expression of microbial pathogenic factors alone may not be sufficient to cause periodontitis[3]. Periodontal pathogens produce harmful by-products and enzymes that break extracellular matrices as well as host cell membranes to produce nutrients for their growth. In doing so, they initiate damage directly or indirectly by triggering host-mediated responses that lead to self-injury. In the early phase of the disease (gingivitis), inflammation is confined to the gingivae but extends to deeper tissues in periodontitis, leading to gingival swelling, bleeding, and bad breath. In the late phase of the disease, the supporting collagen of the periodontium degenerates, the alveolar bone begins to resorb and gingival epithelium migrates along the tooth surface forming a "periodontal pocket".[4,5] This periodontal pocket provides ideal conditions for the proliferation of microorganisms: primarily Gram-negative, facultative anaerobic species. Prominent amongst these are *Bacteroidesspp; B. intermedius and B.gingivitis; fusiform organisms*:*'Actinobacillus actinomycetes comitans, Wolinella recta*,and*Eikenella spp.;* and various bacilli and cocci; spirochetes; amoebas and *trichomonas*. [6]

The periodontal pocket, however, remains and if it continues to harbor the bacteria associated with the disease, a potential for a further destructive phase exists. The Disease may then require extensive treatment, failing which the teeth may be lost. Therefore, clearance of the subgingival infection and elimination of the periodontal pocket is considered a priority in the treatment of periodontitis. [7,8]

MATERIALS AND METHODS

Metronidazole was obtained as a gift sample. Pluronic-F-127 was obtained as a gift sample from BASF India Ltd. Xanthan gum, Methyl Paraben, and Carbopol-934 was obtained from Research Lab Fine Chem Industries, Mumbai. HPMC-K100 was obtained as a gift sample from Coloricon Asia Pvt. Ltd, Verna, and Goa.

METHOD:

- **Preliminary study**

Preformulation studies are the first step in the rational development of the dosage form of a drug substance. The objective of Preformulation studies is to develop a portfolio of information about the drug substance that is useful to develop the formulation. Preformulation can be defined as the investigation of the physical and chemical properties of drug substances alone and when combined with excipients[8,9].

Compatibility Study

Drug polymer compatibility testing was performed by mixing drugs with polymer in equal proportion and the IR spectrum was noted for the mixture. [9]

Formulation Optimization

To achieve the formulations with desired gelation temperature, viscosity, rheology, *in-vitro* drug release, and syringe ability, the formulations were prepared by using different concentrations of Xanthan gum, carbopol-934, HPMC-K-100 and were evaluated.

Preparation of *in-situ* gelling system:

Aqueous Solution of varying concentrations containing Carbopol 934 and HPMC K-100, Xanthan gum were prepared and evaluated for gelling capacity and viscosity to identify the composition suitable for as *in–situ* gelling system (Formulation codes F1,F2,F3,F4,F5,F6,F7,F8,F9,F10). Many experiments were conducted by varying the concentration of these polymers to identify the optimum concentration required for the gel formation.

Xanthan gum solutions of various concentrations were prepared by adding the gum to de-ionized water containing, Pluronic-F-127, 0.03% Methyl Paraben. The mixture was stirred by using a magnetic stirrer to ensure thorough mixing. The pH of the gel (1g) was determined using a calibrated pH meter. The values were taken as an average of 3 reading.

Preparation of *in-situ* periodontal gel formulations:

The composition of different gel formulations is shown in Table No. 1.

The *in-situ* gel of Metronidazole was prepared by the cold method. Accurately weigh a Pluronic-F-127 and incorporate it into cold water (Solution A). Then required amount of drug partially dissolved in water was added. Humectant, preservative was added, with continuous stirring, until a transparent solution was obtained (Solution B). The solution of Mucoadhesive polymer was prepared and stirred constantly (Solution C). Then the dispersion was stirred on a magnetic stirrer until a clear solution is not achieved. Then all the solutions were mixed and stirred constantly. All the formulations were stored. [10,11,12]

Table No. 1: Composition of Periodontal Gel Formulation

Sr. No.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Drug(mg)	120	120	120	120	120	120	120	120	120	120
2	Pluronic F-127	18	18	18	18	18	18	18	18	18	18
3	Xanthan gum	-	0.10 %	0.15 %	0.25 %	-	-	-	-	-	-
4	HPMCK100	-	-	-	-	0.10 %	0.15 %	0.25 %	-	-	-
5	Carbopol 934	-	-	-	-	-	-	-	0.10 %	0.15 %	0.25 %
6	Methyl paraben (%)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
7	Triethanolamine	-	-	-	-	-	-	-	q.s.	q.s.	q.s.
8	Distilled water	15ml	15ml	15ml	15ml	15ml	15ml	15ml	15ml	15ml	15ml

Evaluation of Periodontal *in-situ* gel:

1) Sol-Gel transition temperature and gelling time

Sol-Gel transition temperature was measured for a solution in a test tube which was put in a low-temperature heating bath and temperature was increased at a rate of 1˚Cevery 5 minutes from 33ºC to 40 ºC Test tube was observed for the formation of a viscous gel. The gelling time was measured by using a glass plate maintained at 37 ºC± 0.5 º C temperatures. The individual formulations (200µl) were dropped on the glass plate (37ºC ±0.5ºC) and gelling time was measured. The transition of solution to viscous gel was observed visually.[13,14,15]

2) Measurement of Gel Strength

A sample of 50 gm of gel was placed in a 100 ml graduated cylinder and gelled in a thermostat at 37 ºC. The apparatus for measuring gel strength (weigh or apparatus as shown in Figure No. 1, weighing 27 gm) was allowed to penetrate in the pluronic-F-127 gel. The gel strength, which means the viscosity of the gel at physiological temperature, was determined by the time (seconds), the apparatus took to sink 5cm through the prepared gel. [16.17]

3) Mucoadhesive force

The mucoadhesive force of all the optimized batches was determined as follows, a section of mucosa was cut from the chicken cheek portion and instantly fixed with mucosal side out onto each glass vial using a rubber band. The vial with chicken cheek mucosa was connected to the balance in an inverted position while the first vial was placed on a height-adjustable pan. The oral gel was added to the nasal mucosa of the first vial. Then the height of the second vial was so adjusted that the mucosal surfaces of both vials come in intimate contact. Two minutes of contact were given. Then weight was kept rising in the pan until vials get detached. The mucoadhesive force was the minimum weight required to detach two vials. The cheek mucosa was changed for each measurement. [1,18]

4) Determination of pH

The pH of the gel was determined using a calibrated pH meter. The readings were taken for an average of 3. [4,19,20]

5) Syringeability

The 5ml of the formulation was passed from a 21 gauge syringe. [21]

6) Drug content uniformity

The vials (n = 3) containing formulation were properly shaken for 2–3 min. One milliliter of the formulation was transferred into a 100 ml volumetric flask with a 1ml calibrated graduated pipette. Fifty milliliters of simulated saliva with pH 6.8 were added. The formed gel was completely crushed with the help of a glass rod followed by vigorous shaking until the formed gel gets completely dispersed to give a clear solution. The final volume was adjusted to 100 mL with simulated saliva. The obtained solution was filtered through a 0.45-micron filter membrane. Ten milliliters of this solution were transferred to a 100 mL volumetric flask and volume was adjusted with simulated saliva. The drug concentration was determined at 300 nm by using Pharmaspec UV-1650 (UV-Visible Spectrophotometer by Shimadzu, Japan). [6,22,23]

7) Viscosity Studies

The viscosity was estimated by using Brookfield viscometer (RVDV-II +Pro) for solutions of Metronidazole at a temperature below 10 ºC by using small sample adaptor spindle No. S21 as well as the preformed gels of these solutions at temperature 35 – 37 ºC by using spindle No.S93 at 1-100 RPM. Evaluations were conducted in triplicate.[10,24]

8) Zone of inhibition

28 gm of agar was suspended in 1000 ml distilled water. Heat to boiling until the medium was dissolved completely. Sterilization was carried out by autoclaving at 15lb (120) for 15 min., poured into a sterile Petri dish. The test bacterium was seeded in the medium and wells were dug into the agar plate with sterile borer. Then antibiotic was added to it. The drug was allowed to diffuse and observed the effect of the drug on seeded bacterium in the form of the zone of inhibition. [22,24]

9) *In-vitro* diffusion study

In- vitro diffusion studies were carried out for all the formulations (F1–F10) using the dialysis technique. One end of pretreated dialysis membrane tubing (5 cm in length) was tied with thread

and 1 ml of the formulation was placed in the dialysis bag and the temperature was maintained to form a stiff gel. The other end of the tubing was also secured with thread and was dipped in a vial containing 30 ml of dissolution medium, closed with a rubber closure. The vials are kept at 37 ± 0.5 ºC in a hot air oven. Aliquots were collected periodically and replaced with a fresh dissolution medium. Aliquots, after filtration through Whatman filter paper (No. 41), were analyzed spectrophotometrically at 300 nm for metronidazole content using UV-1650 (UV visible spectrophotometer by Shimadzu, Japan). [18.23]

RESULTS AND DISCUSSION

1) Viscosity:

Showed polymer concentration-dependent rise in viscosity. It is seen that as the concentration of bioadhesive polymer increases, viscosity increases proportionally. The pluronic gel shows a thermoreversible property. The Pluronic gel at cold temperature converts into liquid form. As the temperature of the system increases the liquid form converts into gel at room temperature. Thus, Pluronic gel shows the temperature-dependent thixotropic behavior. The result was recorded.

2) Gel strength:

In the present study, it was found that the addition of bioadhesive polymers increased the gel strength of the Pluronic-F-127 mixture in a concentration-dependent manner. Out of the three Mucoadhesive polymers, Xanthan gum exhibited higher gel strength. In the comparison of a formulation containing no bioadhesives the average increase gel strength noticed with all the bioadhesive polymers used can be arranged in the following order Xanthan gum > Carbopol 934 > HPMC K 100. The results are shown in Table No. 2.

Table No. 2: Gelling time, Gelling temperature, pH, Syringeability, Viscosity, and %Drug content of prepared Formulations

Sr. No.	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Gelling time	-	25 - 30	35 - 40	40 - 42	50 - 52	52 - 53	54 - 56	30 - 35	35 - 38	36 - 37
2	Gelling temperature	-	53	44	40	57 - 60	52	65 - 68	43 - 44	44 - 45	42 - 43
3	pH	6.8	6.83	6.84	6.72	6.73	6.7	6.75	6.84	6.8	6.85
4	Syringeability	+++	+++	+++	+++	+++	++	+++	+++	+++	+++
5	Clarity	***	***	***	**	***	**	*	**	**	***
6	Drug content (%)	96.7	87.09	89.03	89.67	96.4	90.9	93.1	96.12	95	96.77
7	Gelling strength	-	6 – 7 sec	5-6 sec	8-9 sec	4-5 sec	3-4 sec	4 – 5 sec	5 – 6 sec	4 – 5 sec	4 – 5 sec

3) pH:

The values of the pH were within the range of neutral pH, this indicates formulation can be used without any irritation to the oral cavity. Table No. 2 shows that the pH values of all the formulations are in the range of 6.7-6.83. The results are shown in Table No. 2 above.

4) Syringeability:

All the formulations passed through the syringe of gauge 21. Above the concentration of 0.25%, the gel becomes too much viscous and cannot pass through the syringe. The results are shown in Table No. 2.

5) Drug content-

The percentage drug content of all batches was found between the range 87 % to 96.70 %, which was within the acceptable limit which indicated dose uniformity in each batch, which is shown below:

Table No: 3 Percentage drug release (%)

Sr. No.	Time (hrs)	Percentage Drug release (%)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	0	0	0	0	0	0	0	0	0	0	0
2	1	4.89 ± 0.01	20.02 ± 0.02	17.86 ± 0.02	15.70 ± 0.01	20.02 ± 0.02	15.70 ± 0.03	17.86 ± 0.04	17.86 ± 0.04	20.02 ± 0.03	15.70 ± 0.04
3	2	9.21 ± 0.03	22.18 ± 0.03	22.18 ± 0.04	26.50 ± 0.02	30.82 ± 0.03	24.34 ± 0.04	28.66 ± 0.06	24.99 ± 0.05	26.50 ± 0.05	24.99 ± 0.05
4	3	17.86 ± 0.05	28.66 ± 0.03	26.50 ± 0.05	30.82 ± 0.03	39.47 ± 0.06	35.15 ± 0.02	37.31 ± 0.08	31.26 ± 0.07	31.90 ± 0.07	26.93 ± 0.06
5	4	22.18 ± 0.06	35.15 ± 0.05	36.15 ± 0.07	39.47 ± 0.05	45.95 ± 0.04	41.63 ± 0.05	43.79 ± 0.02	34.71 ± 0.08	35.58 ± 1.2	29.09 ± 0.07
6	5	26.93 ± 0.08	45.95 ± 0.07	43.79 ± 0.09	45.95 ± 0.04	54.59 ± 0.02	48.11 ± 0.06	50.27 ± 1.2	36.66 ± 1.2	39.03 ± 1.4	34.28 ± 0.08
7	6	30.82 ± 0.09	50.27 ± 0.08	52.43 ± 0.05	52.43 ± 0.02	61.08 ± 0.04	52.43 ±	52.43 ± 1.4	48.11 ± 1.4	48.11 ± 1.5	48.11 ± 2.1
8	7	35.15 ± 0.12	58.91 ± 0.09	56.75 ± 0.04	56.75 ± 0.06	67.56 ± 0.05	65.40 ±	58.91 ± 1.6	52.43 ± 1.6	52.43 ± 1.7	55.46 ± 2.3
9	8	45.15 ± 0.14	63.24 ± 1.0	61.08 ± 0.03	59.24 ± 0.04	72.53 ± 0.07	69.72 ±	67.56 ± 1.7	57.19 ± 1.7	57.19 ± 1.9	61.08 ± 2.4
10	9	50.27 ± 0.15	65.40 ± 1.2	63.424 ± 0.02	65.40 ± 0.03	74.04 ±0.09	76.20 ±	74.04 ± 0.03	67.56 ± 1.8	60.21 ± 2.0	65.40 ± 2.5
11	10	51.15 ± 0.15	71.88 ± 1.4	67.56 ± 0.06	67.56 ± 0.05	77.28 ± 1.2	79.44 ±	77.50 ± 0.05	74.47 ± 2.1	64.96 ± 2.1	74.47 ± 2.7
12	11	55.67 ± 0.16	74.04 ± 1.5	71.88±0.08	70.15 ± 0.03	82.68 ± 1.4	80.52 ±	79.87 ± 1.7	79.87 ± 2.3	74.04 ± 2.3	79.49 ± 2.2
13	12	60 ± 0.17	76.63 ± 1.6	74.04±0.07	72.53 ± 0.01	87.01 ± 1.6	82.68	82.25 ± 1.8	82.68 ± 0.01	84.84 ± 2.4	80.52 ± 2.3
14	13	65.40 ± 0.18	79.66 ± 1.7	76.42±0.06	74.90 ± 0.03	89.17 ± 1.4	89.60	85.28 ± 2.4	92.42 ± 0.05	91.76 ± 2.6	89.17 ± 2.4
15	14	69.73 ± 0.10	81.69 ± 1.9	79.94±0.05	77.93 ± 0.07	92.14 ± 1.2	91.33	90.25 ± 2.6	96.95 ± 0.07	95.65 ± 2.8	94.57 ± 2.5

The drug release profile of gel formulation F2-F10 was obtained by varying concentrations of Xanthan gum, HPMC-K-100, Carbopol-934.

Release profile indicates that with increasing the concentration of bioadhesive polymer, drug release rate decreases which may be due to the formation of complex matrix and thus increases path length for a drug to travel. The *in-vitro* drug release was found to be decreased from 92.41 to 90.25 % for HPMCK-100, 81.69 to77.93 for Xanthan gum, 96.95 to 94.95 for Carbopol-934, with an increasing polymer concentration of 0.10% - 0.25 % in duration of 14 hr.

6) Mucoadhesive force:

Mucoadhesive strength was determined by measuring the force required to detach the formulation from the mucosal surface i.e., detachment stress. Results reveal that variable polymer is affecting mucoadhesive strength. The test was performed on an optimized batch on basis of *in –vitro* diffusion study. Result was recorded.

7) Antimicrobial study

S.aureus is a part of human flora. *S. aureus* is not the main periodontal pathogen that induces periodontitis. In this study, *S. aureus* was only used as a model bacteria to prove the effectiveness of formulated gel in releasing the metronidazole content and killing bacteria.

The results of the antibacterial studies of all formulations against *S. aureus* using the agar diffusion method and zone of inhibition were recorded. The antimicrobial activity was determined by measuring the zone of inhibition against *S. aureus* bacteria. The results of all formulations were satisfactory as the greatest activity was observed with the F-10 formulation. The lowest activity was found with F2 formulation.

8) Stability study

The purpose of stability testing is to provide evidence of how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and to establish a retest for the drug substance or shelf life for the drug product and recommended storage conditions. The storage conditions used for stability studies were room temperature (37ºC ± 2 ºC/65 % RH ± 5 %). A stability study was carried out for the optimized formulations. The gel of the optimized formulation was packed and kept in a humidity chamber for 30 days at above mention temperature. It was found that the formulation passes the test.

Test performed

- *In-vitro* diffusion study
- Drug Content

9) Compatibility study

From the FT-IR spectra of Metronidazole and mixture, it can be seen that there is no change in the significant peak of Metronidazole in the mixture indicating the stability of the drug in the formulation mixture.

Drug-Excipient Compatibility Studies

Any formulation development work has to be proceeded by Preformulation studies. This Preformulation study includes drug-excipients compatibility deliberate by DSC and FT-IR analysis. FT-IR study showed that there was no major change in the position of peak obtained in the drug alone and in a mixture of the drug with excipients, which shows that there was no interaction between drug and excipient. Results are shown in Figure:

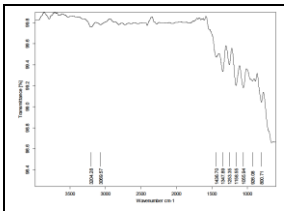	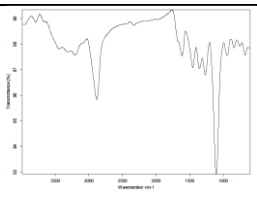	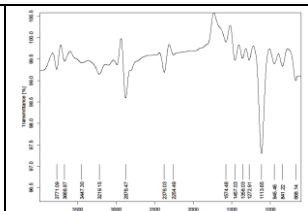	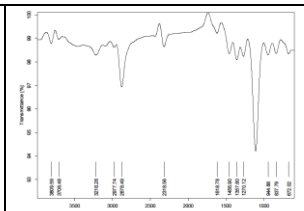	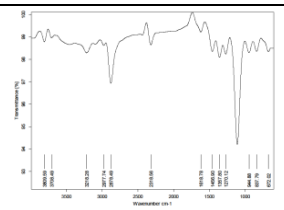
Fig No-1:FT-IR Spectrum of Metronidazole	Fig No-2:FT-IR Spectrum of Metronidazole+ Pluronic-F-127	Fig No-3: FT-IR Spectrum of Metronidazole + Xanthan gum+Pluronic-F-127	Fig No-4: FT-IR Spectrum of Metronidazole +Carbopol +Pluronic-F-127	Fig No-5: FT-IR Spectrum of Metronidazole HPMC-K100 +Pluronic-F-127

Figure: Compatibility Study FT-IR Spectrum

In addition, it is remarked that the DSC thermogram of Metronidazole is characterized by one sharp endothermic peak at about 166 ºC which corresponds to the melting point of the drug. But, there may be an interaction of drug with polymer Carbopol, HPMC-K-100, Xanthan gum, Pluronic-F-127, due to which there may be a slight change in the physicochemical property of Metronidazole drug. As the heat was absorbed, the drug with the mixture undergoes an endothermic reaction. So, a slight change in the peak was seen i.e. melting point of the drug was decreased. Results are shown in Figure.

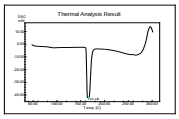	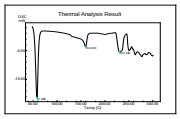	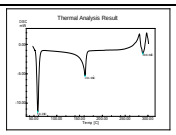	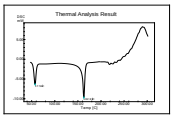	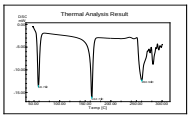
Fig No-6– DSC Spectra of pure Drug	Fig No-7 – DSC Spectra of pure Drug+Pluronic F-127	Fig No-8- DSC of Pure drug +Pluronic F-127+ HPMC-k100	Fig No-9 DSC of Pure drug +Pluronic F-127	Fig No- 10 - DSC of Pure drug +Pluronic F-127+ Carbopol

Figure: Result of DSC (`Differential scanning Calorimetry)

10) Stability study

The purpose of stability testing is to provide evidence of how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The storage conditions used for stability studies were room temperature (37 ºC ± 2 ºC/65 % RH ± 5 %). Stability study was carried out for the optimized formulations. Gel of optimized formulation were packed and kept in humidity chamber for 30 days on above mention temperature. It was found that formulation passes the test.

Test performed

- In-vitro diffusion study
- Drug Content

DISCUSSION:

In present research work *in situ* periodontal gel containing Metronidazole was developed with the combination of Carbopol-934, Xanthan gum, HPMC-K100, and poloxamer 407 using ion-sensitive and temperature-sensitive approaches. By doing a compatibility study, the drug was found to be compatible with formulation excipients, it is concluded that the selected polymers are likely to be suitable for preparation of *in situ* periodontal gel formulation. The developed formulations show satisfactory results for gelation time, gelation temperature, syringeability, and

other physical properties. Based on maximum desirability and cost-effectiveness formulation containing 0.25%W/V of Carbopol-934 and poloxamer 407 was considered as an optimized formulation.

CONCLUSION:

Metronidazole as local drug delivery may be an advantageous form of treatment since it would probably eliminate side effects, which occur with systemic dosing. So in the present research work, an attempt has been made to formulate an *in-situ* gel of Metronidazole for the effective management of periodontitis with local delivery into the periodontal pockets. *In-situ* gel implants of Metronidazole with Mucoadhesive polymers such as HPMC K-100, Carbopol 934, and Xanthan gum were formulated. The major advantage of Pluronic-F-127 is its thermoreversible nature that is used for *in-situ* gel formulation. From the present study, it can be concluded that the developed formulation is having enough Mucoadhesive property, it will remain in the cavity for sufficient time, which can again be protected by periodontal dressing. The local drug delivery system in the present study is simple and easy to use. Its syringeability allows easy insertion of gel formulation into the periodontal pocket. The developed formulation can release the drug at a controlled rate for a prolonged duration. The results indicate that these targeted devices for the treatment of periodontal diseases show significant advantages over conventional therapy. Effective and prolonged local levels of an anti-microbial could be achieved without much systemic load with comparatively less frequency of administration. This type of drug delivery system can serve as a new approach for treating periodontal disease with better patient compliance.

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