FORMULATION AND EVALUATION OF *IN SITU* GEL FOR THE TREATMENT OF PERIODONTAL DISEASE

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ABSTRACT

Periodontitis is a chronic inflammatory disease affecting supporting tissues of teeth. Conventional treatment is the systemic administration of antibiotics which requires repeated dosing and resulted in toxic adverse effects. These consequences can be solved by delivering the drug at the desired target site to show local therapeutic action. *In situ* gel-forming systems are polymeric system that exists as flowing solution before administration and undergoes phase transition to form a viscoelastic gel in a physiologic environment. Aim of the present work was to formulate and evaluate an *in situ* gelling drug delivery system of ofloxacin by cold method using the polymers poloxamer 407 and carbopol. The prepared *in situ* gels were evaluated for visual inspection, surface pH, viscosity, syringeability, gelation temperature, gelling time, *in vitro* gelling capacity, drug content and *in vitro* drug release. The formulation F4 was selected as the optimized formulation which has a gelation temperature of $36.33\pm0.57^{\circ}$C with drug content of $95.92\pm0.13\%$ and showed *in vitro* drug release of 72.59% at the end of 8 hrs. It follows first order release kinetics with Higuchi model drug release mechanism. The selected formulation was evaluated for its antibacterial activity and stability and it showed good antibacterial activity against both gram positive and gram negative microorganisms and was stable at refrigerated temperature over three months.

KEYWORDS: *In situ*, Periodontitis, poloxamer, carbopol, ofloxacin, *in vitro*, thermoreversible.

INTRODUCTION

Periodontal diseases are heterogeneous group of diseases characterized by inflammation and subsequent destruction of tooth supporting tissues. It is a localized inflammatory response caused by bacterial infection of a periodontal pocket associated with subgingival plaque. The two types of periodontal disease includes gingivitis and periodontitis. Gingivitis is a chronic inflammatory process limited to the gingiva without either attachment loss or alveolar bone loss. When gingivitis is left untreated it progresses to periodontitis, leading to irreversible destruction of tissues and bone that support the teeth (Neha bisht et al.,2014). Periodontal diseases are of an infectious nature and that the microorganisms present in the subgingival bacterial plaque are the primary etiologic agents. If the plaque is not removed, it can turn into a hard substance called calculus or tartar in less than two days. The bacteria in the plaque infect the gums, and release poisons that cause redness and inflammation. The inflammation and the poisons themselves cause destruction of the tissues that support the teeth, including the bone. When this happens, the gums separate microscopically from the teeth, forming pockets that fill with even more plaque causing even more infection.

Antibacterial agents are used effectively in the management of periodontitis. 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. They also caused systemic side effects. Hence local delivery of antimicrobials has been investigated which deliver the antibacterials to site of infection (periodontal pocket) to provide long term effective treatment at the site at much smaller doses. The development of *in situ* gel systems for treatment of periodontal disease has received considerable attention over the past few years. This interest has been sparked by the advantages shown by the *in situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. *In situ* gel forming polymeric systems are novel drug delivery systems which are in solution form before administration in the body, but once administered, undergo gelation *in situ*, to form a gel. *In situ* gel drug delivery system possess potential advantages like ease of administration, reduced frequency of administration, improved patient compliance by decreasing dosing frequency, and increase local bioavailability. They reduce systemic side effects associated with antibiotics (Swapnil S et al.,2014). Formation of gel in the peridontium can prolong drug action and achieve sustained drug release. The difficulties associated with tablets and capsules can overcome by using this *in situ* gel system.

In present study an attempt was made to develop a sustained release *in situ* gel of ofloxacin for treating periodontitis using poloxamer and different concentrations of carbopol. This study aims to increase the bioavailabilty and reduce the dose and frequency of administration.

MATERIALS AND METHODS

Ofloxacin and poloxamer 407 were obtained from Yarrow chem products, Mumbai and carbopol was obtained from Lobachemie Pvt Ltd. All other ingredients used were of analytical grade.

All the equipments and instruments were of standard quality and calibrated.

METHODS

Preformulation studies: Preformulation studies are the first step in the rational development of dosage forms. It is done to establish the identity and purity of drug and the excipients and to find out if any interaction exist between the drug and excipients used. The preformulation studies conducted includes determination of melting point and determination of physicochemical properties. Melting point was determined using capillary fusion method.

Analytical methods

Determination of λmax: The standard solution of ofloxacin (10µg/ml) was scanned in the wavelength region of 200- 400nm and determined the wavelength at which maximum absorbance was observed.

Preparation of calibration curve of Ofloxacin: The working standard solutions of ofloxacin (2-10µg/ml) were scanned in the UV region and the absorbances were observed against phosphate buffer (pH 6.8) solution as blank at 293nm. Finally the calibration curve was plotted with concentration on X axis and respective absorbances on Y axis (shaik firoz et al., 2014).

Drug excipient compatibility studies

Preformulation studies regarding the drug-polymer interaction is very important in the selection of appropriate polymers. So the integrity and compatibility of pure drug ofloxacin with the polymers were studied using Fourier Transformed Infra-red Spectroscopy (FTIR). The FTIR spectra of pure drug, polymers and the physical mixture of drug and polymers were taken. The spectra was run between $4000 - 500 \text{cm}^{-1.}$

Formulation of *in situ* gel of ofloxacin

Thermoreversible gels of ofloxacin were prepared using cold method. *In situ* gels were prepared using thermosensitive polymer poloxomer 407 and mucoadhesive polymer carbopol 934. The poloxomer 407 vehicles used throughout this study were composed of 18%w/v of poloxamer 407 until a clear solution was obtained.

Poloxamer 407 was slowly added in cold water with continuous agitation and the formed mixtures were stored overnight at 4^0C. Carbopol 934 was also kept overnight to allow sufficient swelling. Slowly added the carbopol solution to poloxamer solution with continuous agitation. To the above mixture added specified quantity of drug and mixed well. The mixtures were kept overnight at 4°C to effect complete hydration (Parvathy S et al.,2015) The compositions of prepared formulations were shown in Table 1.

Evaluation of *in situ* gel

Visual appearance: Gel formulations were visually inspected for clarity, colour and homogeneity.

Surface pH: The pH of prepared formulations were determined using a digital pH meter. It was calibrated using a buffer solution having pH of 4.0, 7.2 and 9.0. After that pH was noted by bringing the electrode near to the surface of formulations and allow it to equilibrate for 1 min (Revathy V Nair et al., 2014).

Viscosity

The viscosity of each formulation at room temperature (25±5°C) was noted using Brookfield viscometer DV-I-LV. The measurements were carried out using spindleno.62 at a speed of 50 rpm. A sample of 400 - 600ml in a suitable container is placed under the viscometer which is then lowered to dip the spindle into the sample up to an immersion mark on the spindle shaft. Viscometer motor rotates the spindle at a defined speed (measured in rpm) or shear rate and the viscometer measures the resistance to rotation and reports a viscosity value. The measurements were taken in triplicate.

Syringeability

All prepared formulations were transferred into an identical 5 ml plastic syringe placed with 21 gauge needle to a constant volume (1 ml). The solutions which were easily passed from syringe was termed as pass and difficult to pass were termed as fail (Parvathy S et al., 2015).

Gelation temperature

2 ml aliquot of gel was transferred to test tube and immersed the test tube in a water bath. The temperature of water bath was slowly increased and was left to equilibrate for 5 min at each new setting. The sample was then examined for gelation which was said to have occurred when the meniscus would no longer moves upon tilting through 90°c. Each sample was measured in triplicate (Wedian Younis Abdelgawad et al., 2016).

Gelation time

2 ml of formulation was taken in a 15 ml borosilicate glass test tube and was placed in a water bath which is maintained at 37 ± 2^0C. The gelation time was noted when there was no flow of gel when the test tube was inverted (Wedian Younis Abdelgawad et al.,2016).

***In vitro* gelling capacity**

To study the *in vitro* gelling capacity of prepared formulations, simulated saliva is used. 2ml of simulated saliva was placed in a 15 ml borosilicate glass test tube and maintained at 37 ± 2^0C. 1ml of formulation to be evaluated was added with a 1ml pipette. The formulation was added in such a way that places the pipette at the surface of fluid in test tube and was released slowly. As the formulation comes in contact with the simulated saliva it was immediately converted to a stiff gel like structure. The gelling capacity was evaluated on the basis of stiffness of formed gel and time it remains as such. The *in vitro* gelling capacity was given three grades (+) gelation after few minutes, dispersed rapidly, (++) gelation immediate, remains for few hours and (+++) gelation immediate, remains for an extended period (Gorle Ashish et al., 2017).

Drug content

1ml of each formulation was taken in 10 ml volumetric flask, diluted with distilled water and make up the volume to 10ml. 1ml of solution was taken and diluted to 10ml with distilled water. Measured the absorbance of final solution at 293 nm using double beam UV visible spectrophotometer (Gorle Ashish et al., 2017).

***In vitro* drug release**

In vitro drug release study was performed by static dissolution method since the *in situ* gel should be immobile in the periodontal pocket. Phosphate buffer pH 6.8 was used as the dissolution medium. The receptor compartment was filled with 20ml of dissolution medium. The pretreated egg membrane was mounted on one end of diffusion tube which act as donor

compartment and placed 2ml of formulation inside the tube. The whole diffusion assembly was then placed in the thermostatically controlled magnetic stirrer. At predetermined time intervals 2ml of aliquots were withdrawn carefully from the receptor compartment and analysed spectrophotometrically at 293 nm. The medium was replaced immediately with the same volume of fresh phosphate buffer maintained at 37±0.5˚C (Priyanka M.Borole et al., 2013).

Selection of best formulation

Out of seven formulations one formulation is selected as the best formulation based on gelation temperature, Viscosity, *In vitro* drug release and drug content.

***In vitro* antibacterial study of optimized formulation**

The antimicrobial efficiency of optimized formulation was studied using microorganisms *Staphylococcus aureus* and *Escherichia coli* by agar well diffusion method. Nutrient agar medium was prepared and sterilized by autoclaving and inoculated with 0.1ml of fresh overnight nutrient broth culture of each bacterium in separate flasks and were poured into sterile petriplates. Allow them to solidify. After solidification cups were made on each plates with the help of sterile borer of 6mm diameter. Poured appropriate amount of formulation and pure drug solution to the cups and incubated for 24 hrs at 37˚C. The diameters of the zones of inhibition were measured and compared with that of standard (Hareesh Babu Kunche et al.,2012).

Release kinetics

To analyze the mechanism of drug release kinetics the obtained data were fitted to various kinetic equations including zero order, first order, Higuichi and korsmeyer peppas models. The best fit model was selected on the basis of relatively high co-relation coefficient (Suvakanta Dash., 2010).

Stability studies

The stability studies were carried out to determine the physical and chemical stabilities of prepared formulations. The optimized formulation were kept in air tight container covered with aluminium foil at refrigerated temperature, 4˚C for a period of 3 months. The formulation was evaluated visually and for its gelation behaviour, viscosity, drug content and *in vitro* drug release.

RESULTS

Preformulation studies: From the preformulation studies conducted, melting point of pure drug ofloxacin was found to be 254± 0.42 ˚C. The absorption maxima of ofloxacin was found to be 293 nm. The calibration curve of ofloxacin in phosphate buffer is prepared and is shown in fig 1. The curve was found to be linear and thus obeyed Beer Lambert's law. From the FTIR spectra of drug- polymer mixture and that of pure drug, it was found that there were no major differences seen in the characteristic absorption peaks of pure drug.

Surface pH: An acidic or alkaline formulation is bound to cause irritation on mucosal membrane, and hence this parameter assumes significance while developing a mucoadhesive formulation. The pH of all formulations were found within range 6.0- 7.2 and this pH range is suitable for insertion into periodontal pocket without any irritation.

Viscosity: Viscosity of prepared formulations was measured using Brookfield viscometer. All the prepared formulations should have sufficient viscosity to be applied in the periodontium so that it will remain in the periodontal cavity to have sustained release of drug. The viscosity of formulations ranges from 281±3.60 - 743±11.37 cp.

Syringeability: The prepared *in situ* gel of ofloxacin is to be applied with a syringe into the periodontal cavity. The syringeability of the formulation is presented as pass or fail after passing through a syringe attached with 21 gauge needle. All the formulations passed the syringeability test. The viscosity of formulations at cold temperature is such that they can be easily passed through the syringe. Results revealed that all formulation from F1 to F7 were syringeable at cold temperature.

Gelation temperature: The sol- gel transition temperature of formulations is noted to find out their ability to form *in situ* gel inside the oral cavity. The gelation temperature was found in the range of 33 ± 1^0C –36.33 ± 0.57^0C.

Gelling time: The time required for the solution to form gel is recorded in seconds. The gelling time was found to increase with increasing concentration of carbopol. The gelation time was found to be in the range 33±1.52 - 102±2.64 seconds.

***In vitro* gelling capacity:** The formulations should undergo rapid sol to gel transition in simulated saliva and the formed gel should preserve its integrity without eroding or dissolving. The formulations were evaluated for *in vitro* gelling capacity in simulated saliva.

The *in vitro* gelling capacity was given in three grades (+) gelation after few minutes, dispersed rapidly, (++) gelation immediate, remains for few hours and (+++) gelation immediate, remains for an extended period. All the formulations except F6 and F7 showed immediate gelation and remained for few hours when come in contact with simulated saliva maintained at 37 ± 2^0C. Formulations F6 and F7 showed gelation after few minutes and were dispersed rapidly.

Drug content

Drug content of the formulations were estimated using UV- visible spectrometer. The drug content was found in the range of $82.98\pm0.44 - 95.92\pm0.13\%$. The formulations exhibit fairly uniform drug content. Formulation F4 showed maximum drug content of 95.92%.

***In vitro* drug release**

The release studies of prepared in situ gelling systems were carried out up to 8 hours using phosphate buffer (pH 6.8) and the cumulative percentage drug released was calculated. The release rate was found to increase with increasing concentration of carbopol up to an optimum concentration and then found to be decreasing. Formulation F4 showed maximum drug release at the end of 8hrs.

The results of evaluation studies conducted were given in table 2 and 3.

From the evaluation studies conducted on the prepared formulations one formulation was selected as the best formulation. Formulation F4 composed of 18% w/v poloxamer and 0.2% carbopol was selected as the optimized formulation. It has a gelation temperature of $36.33\pm0.57^{\circ}$C, gelling time of 67 ± 1.52 sec and has drug content $95.92\pm0.13\%$. The viscosity of F4 was found to be 527 ± 4.58 and it showed cumulative drug release of 72.59% at the end of 8 hrs. Further studies including drug release kinetics, *in vitro* antibacterial studies and stability studies were conducted on formulation F4.

Kinetics of optimized formulation

The mechanism of drug kinetics of selected formulation F4 were studied using different kinetic models. The data from *in vitro* drug release were fitted to various kinetic equations of zero order, first order, Higuchi model and Korsmeyer-Peppas model. Calculated regression coefficients and is summarized in the table 4. It was found that optimized formulation F4 follows first order kinetics with Higuchi model drug release mechanism.

In vitro **antibacterial study**

The *in vitro* antibacterial activity of optimized formulation (F4) against gram positive *Staphylococcus aureus* and gram negative *Escherichia coli* were carried out using test and standard preparations. The standard was pure drug of ofloxacin in distilled water. The study was carried out for 24 hours using well diffusion technique. The antibacterial activity of formulation was confirmed by the formation of zone of inhibition of microbial growth around the well. Measured the zone of inhibition against each organisms and compared it with the standard. The zone of inhibition of test sample was similar to that of standard for both gram positive and gram negative organisms. This indicates that the prepared *in situ* gel formulation has good antibacterial activity against *Staphylococcus aureus* and *Escherichia coli.* The test sample and standard sample shows a zone of inhibition of 52mm and 45 mm for *E. coli* and 78 mm and 68 mm for *Staphylococcus aureus* respectively.

Stability studies: The optimized *in situ* gel formulation F4 was selected for the stability study and is stored at refrigerated temperature (4∘C) for three months. The formulation showed good stability with no significant changes in the appearance, viscosity, gelation behaviour, drug content and *in vitro* drug release. From the stability study it was confirmed that the optimized formulation is stable at its storage temperature.

Table 1. Composition of in situ periodontal gel.

Sl. No	Formulation code	Poloxamer 407(%w/v)	Carbopol934 (%)	Drug(mg)	Distilled water upto(ml)
1	F1	18	0.05	100	20
2	F2	18	0.1	100	20
3	F3	18	0.15	100	20
4	F4	18	0.2	100	20
5	F5	18	0.25	100	20
6	F6	18	0.3	100	20
7	F7	18	0.35	100	20

Table 2. Gelation temperature and gelling time of formulations.

SL. No	Formulation code	Gelation temperature(^{0}C)	Gelling time(sec)
1	F1	34.33±0.57	33±1.52
2	F2	34±1	46.33±1.15
3	F3	33.66±0.57	59.66±1.52
4	F4	36.33±0.57	67±1.52
5	F5	35.33±0.57	76.33±1.52
6	F6	34±1	93±3.10
7	F7	33±1	102±2.64

 values are mean±sd, n=3

Table 3. Evaluation tests of prepared formulations.

Sl. No	Formulation code	Surface pH	Viscosity(cp)	In vitro gelling capacity	Syringeability	Drug content(%)
1	F1	7.2	281±3.60	++	Pass	90.40±0.57
2	F2	7.1	342±7.09	+++	Pass	94.40±0.33
3	F3	7.0	435±9.64	++	Pass	91.95±0.31
4	F4	6.7	527±4.58	++	Pass	95.92±0.13
5	F5	6.5	592±7.09	++	Pass	95.11±0.31
6	F6	6.2	671±7.02	+	Pass	86.01±0.26
7	F7	6.0	743±11.37	+	Pass	82.98±0.44

values are mean±sd, n=3

Table 4. Regression coefficients of kinetic models of F4.

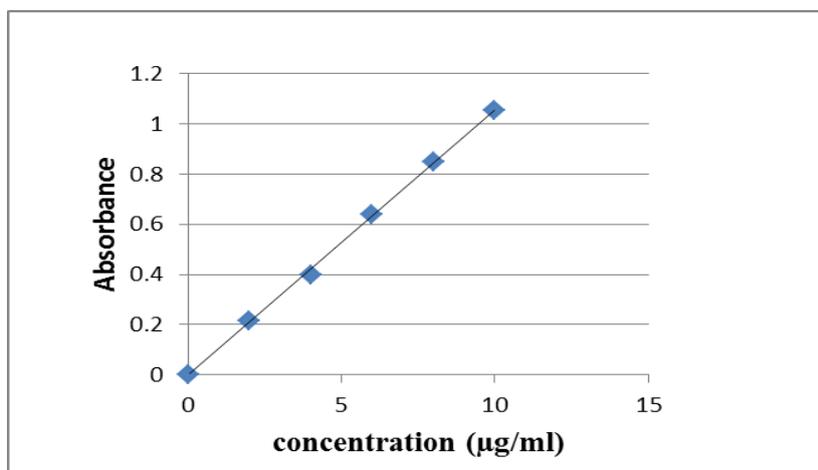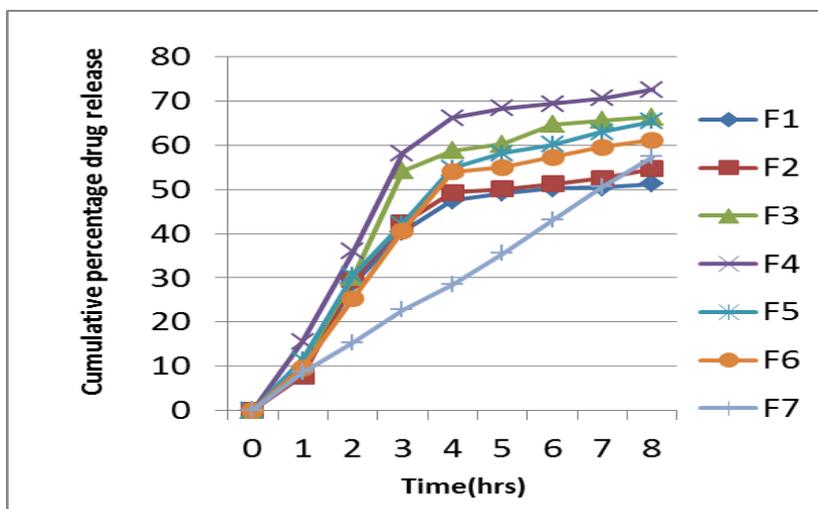| Formulation code	Zero order	First order	Higuchi	Korsmeyer Peppas
F4	0.8069	0.8766	0.9232	0.635

Fig. 1: calibration curve of ofloxacin in phosphate buffer (pH 6.8).

Fig. 2: *In vitro* **drug release profile of formulations.**
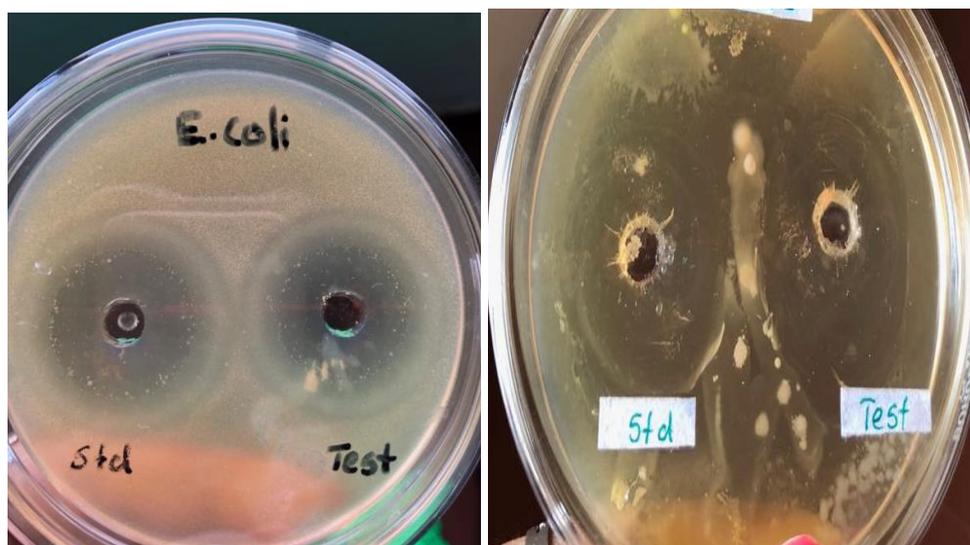
Fig. 3. photograph of _in vitro_ antibacterial activity of F4 against (a) Escherichia coli (b) Staphylococcus aureus.

DISCUSSIONS

The drug was identified as ofloxacin by determining its melting point and from its FTIR spectra. By comparing the FTIR spectra of pure drug and drug-polymer mixture it was found that there were no interaction exist between the drug and polymers. The calibration curve of drug was prepared and found that it obeyed Beer Lambert's law in in that concentration range (0-10μg/ml).

From the visual inspection, all seven formulations were found to be viscous free flowing liquids at their storage temperature 4°C. All formulations except F7 forms soft gel with good consistency. With increase in concentration of carbopol their gelling ability also improves. The pH of _in situ_ formulation should be such that it must be stable at that pH and should not cause any irritation to the patient upon administration. The pH range was between 6.0-7.2. Periodontal mucosa can tolerate this neutral pH and hence the formulations can be applied to periodontal cavity without causing any irritation. The viscosity range lies between 281±3.60 - 743±11.37 cp. The viscosity was found to increase with increasing concentration of carbopol. The syringeability of formulations is important parameter to be evaluated since the formulation is applied with a syringe. All formulations passed the syringeability test.

The sol-gel transition temperature is an important parameter in case of _in situ_ gels.The gelling temperature was in the range between 33 ± 1 –36.33 ± 0.57^0C. Another important parameter is gelling time which assess the time required for the solution to undergo transition to gel in the

periodontal cavity. Reduced gelling time indicates improved gelling capacity. Formulation F7 had highest gelling time while F1 has the smallest. The gelling time was found to increase with increased concentration of carbopol. The *in vitro* gelling capacity was determined using simulated saliva. All the formulations except F6 and F7 showed immediate gelation and remained for few hours. To achieve sustained release of drug in the periodontal cavity the formed gel should preserve its integrity and hence an optimum concentration of polymers should be used to formulate a suitable *in situ* gelling system.

The percentage drug content of all prepared formulations was found to be in the range of 82.98±0.44 –95.92±0.13 %. The formulations exhibit fairly uniform drug content. This is important in relation to batch to batch uniformity and thus efficacy of the preparation. The release studies of prepared *in situ* gelling systems were carried out up to 8 hours using phosphate buffer (pH 6.8). The release of drug from the formulations were characterized by an initial phase of high release (burst effect) followed by slow release. The initial burst release of drug is expected to kill the pathogenic organisms in periodontal pocket followed by controlled release which further inhibit the growth of organisms. From the evaluation studies formulation F4 was selected as the optimized formulation.

The *in vitro* drug release data of F4 was fitted to various kinetic models and found out the regression coefficients. The drug release of F4 showed first order kinetics with Higuchi model drug release mechanism. From The *in vitro* antibacterial study of F4, the antimicrobial activity of prepared periodontal gel was confirmed. It showed good zone of inhibition against both gram positive and gram negative organisms. Hence it proves it efficiency in killing microorganisms associated with periodontal disease and thus providing effective treatment. The stability studies of optimized formulation was done at refrigerated temperature for a period of three months. The formulation was showing good stability with no significant change in gelation and physicochemical properties and *in vitro* drug release profile.

CONCLUSION

Thermoreversible *in situ* gel containing ofloxacin was prepared using thermo sensitive polymer poloxamer 407 and mucoadhesive polymer carbopol 934 by cold method. The formulation F4 was selected as the optimized formulation which has a gelation temperature of 36.33±0.57°C with drug content of 95.92±0.13% and showed *in vitro* drug release of 72.59% at the end of 8 hrs. It follows first order release kinetics with Higuchi model release mechanism. It showed good antibacterial activity against both gram positive and negative

microorganisms and was stable at refrigerated temperature over three months. The prepared *in situ* gel containing ofloxacin can be an innovative and promising approach for the treatment of periodontal disease.

REFERENCES

1. Abdul Mannan, Zeba Begum, Khizra Nishat. Novel ocular sustained release flurbiprofen in situ gels development and in-vitro evaluation. Ejpmr, 2017; 4(9): 459-464.

2. Akshata. I. Shettar, U. B. Bolmal, A. P. Gadad. Formulation and evaluation of pH triggered in-situ ophthalmic gel containing natamycin cyclodextrin inclusion complex. IJPSR, 2016; 6(2): 94-103.

3. Gorle Ashish, Yadav Rahul, Rathod Mukesh, Mali Prakash. Formulation and evaluation of in situ gel containing ciprofloxacin hydrochloride in the treatment of periodontitis. Asian J Pharm Clin Res., 2017; 10(6): 154-159.

4. Hareesh Babu Kunche, Mohammed Gulzar Ahmed, Narayana Charyulu Rompicharla. Development and evaluation of in situ gels of moxifloxacin for the treatment of periodontitis. Indonesian J. Pharm, 2012; 23(3): 141-146.

5. Neha bisht, Laxmi goswami, Preeti kothiyal. In situ gel: A study of dental disease. Indian Journel of Novel Drug Delivery, 2014; 6(3): 208-214.

6. Parvathy S, Arun Unnikrishnan, Oshin P. George and Sreeja C. Nair. Thermoreversible-pH sensitive cephalexin insitu gel for treating periodontal disease. J. Chem. Pharm. Res., 2015; 7(5): 555-567.

7. Patel tarun k, patel vishnu m. Formulation and evaluation of medicated dental pastes for treatment of periodontitis. IJPI, 2013; 3(1): 16-21.

8. Priyanka M.Borole, Yogesh S.Chaudhari, Sanket S.Dharashivkar, Suresh D.Kumavat, Khushbu Shenghani, Pankit R. Shah. Preparation and evaluation of in situ gel of levofloxacin hemihydrate for treatment of periodontal disease. IJPRBS, 2013; 2(3): 185-196.

9. Revathy V Nair,Sreeja C Nair. Cross linked chitosan in situ gel of satranidazole for intra periodontal drug delivery. Int. Res. J. Pharm, 2014; 5(5): 384-391.

10. Shaik. Firoz, T. Shaik Akmal1, K. Sreenath, P. Sudheer Kumar, K. Swetha, K. Sarada. Formulation and evaluation of ofloxacin dental films. International Journal of Research in Pharmaceutical and Nano Sciences, 2014; 3(2): 105-112.

11. Snehal Nikode, Gauri Dixit, Kanchan Upadhya. Insitu gel: Application and uses of polymers. WJPPS, 2016; 5(7): 1638-1658.

12. Suvakanta Dash, Padala Narasimha Murthy, Lilakanta nath,Prasanta Chowdhury. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica - Drug Research, 2010; 67: 217-223.

13. Swapnil S. Khairnar, Abhishek Kumar Singh, Avinash B. Darekar, Ravindranath B. Saudagar. An innovative approach for in situ gelling system for nasal drug delivery: an overview. WJPPS, 2014; 4(1): 334-356.

14. Vidhyaa Kumari, Vignesh Muruganandham. Formulation, Development & characterization of Ofloxacin Microspheres. Indo Global Journal of Pharmaceutical Sciences, 2012; 2(2): 130-141.

15. Wedian Younis Abdelgawad, Magdy Ibrahim Mohamed, Mary Kamal Gad1, Enji Ahmed. Formulation, evaluation and clinical assessment of Gemifloxacin in situ gel for the treatment of chronic periodontitis. Int. J. Pharm. Sci. Rev. Res., 2016; 38(1): 78-85.