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Research Article

FORMULATION AND EVALUATION OF DENTAL FILM FOR PERIODONTITIS

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ABSTRACT
Controlled release local drug delivery systems offer advantages compared to systemic dosage forms for periodontitis. The objective of this research was to design and evaluate sustained release dental films containing lomefloxacin hydrochloride in a non-biodegradable carrier for targeted delivery of drug. Polymer ethyl cellulose was used in the formulation of the dental films. The dental film was then evaluated for various parameters and in-vitro, in-vivo study. The effects of various formulation variables on the drug release profiles from the films were studied to determine optimum formulations. Drug release profile of dental film showed that the film exerted an initial burst release followed by sustained release of the drug and the drug release was well above the minimum inhibitory concentration throughout the time of study. The study suggests that non-biodegradable polymer based dental film of lomefloxacin hydrochloride is a potential local drug delivery device for the treatment of periodontitis.
Key words: periodontitis, lomefloxacin hydrochloride, ethyl cellulose.

INTRODUCTION

Dental diseases are recognized as a major public health problem throughout the world. Since dental diseases may be chronic, long-term treatment is often necessary. The effective use of antibacterial agents for the treatment of periodontal diseases requires an adequate drug concentration at the site of action and a means to maintain that level for a sufficient duration. Controlled release local drug delivery systems offer advantages compared to systemic dosage forms for periodontitis. The objective of this research was to design and evaluate sustained release dental films containing a non-biodegradable polymer for targeted delivery of drug.

The word periodontal literally means "around the tooth." Periodontal disease is a chronic bacterial infection that affects the gums and bone supporting the teeth. Periodontal disease can affect one tooth or many teeth. It begins when the bacteria in plaque (the sticky, colorless film that constantly forms on your teeth) causes the gums to become inflamed. Periodontal diseases range from simple gum inflammation to serious disease those results in major damage to the soft tissue and bone that support the teeth. In the worst cases, teeth are lost.

Supragingival and subgingival plaque play a vital role in the causation of dental caries and periodontal infections respectively. In the diseased state, supporting collagen of the periodontium is destroyed and the alveolar bone begins to resorb. As shown in (Figure -1) the epithelium of the gingiva begins to migrate along the tooth surface forming pockets, which provides an ideal environment for the growth and proliferation of microorganisms[1-4].

In pharmaceutical field novel and controlled drug delivery system are becoming more popular which are capable of improving patient compliance as well as therapeutic efficacy. In general, controlled drug delivery attempts-[6,7]

- To sustain drug action at a pre-determined rate by maintaining a relatively constant effective drug level in the body with concomitant minimization of undesirable side effects.
- Localize drug action by spatial placement of controlled release system adjacent to or in the disease tissue or organ.
- Target drug action by using carriers or chemical derivatization to deliver drug to a particular target site.

Films are matrix delivery systems in which the drug is distributed throughout the polymer and drug release occurs by diffusion and/or matrix dissolution or erosion. The dimensions and shape of the film can be controlled to correspond to the dimensions of the pocket where the film is to be inserted. It can be rapidly inserted into the pocket with minimal pain to the patient. It can be totally submerged in the pocket and can be inserted to the base of the pocket.[8-10]

For designing an ideal drug delivery device, the following criteria should be considered :

- They have to be small, since the average pocket depth is between 6-10 mm and it cannot be exposed beyond gingival margin when inserted in the periodontal pocket.
- It should not cause any interference to the normal oral hygiene which includes tooth brushing, dental flossing and to the dietary patterns.
- The active agent in the device should display therapeutic effectiveness at low doses.
- The antimicrobial drug should be highly specific against the bacteria in the pocket.
- The drug delivery system should effectively regulate the dosage reaching the target sites.

Delivery systems containing between 2-4 mg of the drug with release rates of several micrograms per hours, giving rise to therapeutically effective levels in the gingival fluid are required for the treatment of advanced periodontal disease.

Although the research concerning local drug delivery devices in the treatment of dental diseases is still young, it has attracted much attention . There is great potential in the treatment offered by local drug delivery devices in dentistry and research as proved this to be a promising alternative method of treatment.

MATERIALS AND METHODS

Materials

Lomefloxacin hydrochloride was obtained as gift sample from Nakoda Chemicals Ltd. Hyderabad, India. Different grade of Ethyl cellulose, were obtained from Colorcon Asia Pvt. Ltd., Goa, India. Other materials used in the study were of analytical grade.

Drug-polymer compatibility

The drug-polymer interaction study was carried out by FT-IR spectroscopy. The IR spectrum of combination of drug and

polymer to be used in the formulation was obtained by using FTIR spectrophotometer and compared with the individual spectra of drug and excipients to investigate any possible interactions. The I.R. spectra of mixture of drug and polymer indicated that there is no interaction between drug and polymers, hence polymers were chosen for further investigations[11-14].The scanned graphs were depicted in the respective (Figure 2, 3 and 4).

Formulation of dental film

Different batches of films were prepared using different drug to polymer ratio in order to study the effect of D/P ratio on the rate of drug release from the films.

Periodontal films were prepared by solvent casting technique[15,16]. Glass moulds were used for casting of films. Ethyl cellulose was taken as the main non-biodegradable polymer. Films were prepared by dissolving Ethyl cellulose in chloroform solution, using dibutyl phthalate and PEG-400 as Plasticizers in a beaker using magnetic stirrer to get different concentration of polymeric solutions. Lomefloxacin hcl was added in to the polymeric solution and mixed homogenously using magnetic stirrer in a closed beaker.

After complete mixing the solution was poured into clean labelled glass moulds placed on horizontal plane. The solvent was allowed to evaporate slowly by inverting a glass funnel with a cotton plug closed into the stem of the funnel at room temperature for 24 hours. After complete evaporation of solvent, cast films obtained, which were then cut into pieces of (10×6 mm.), wrapped in an aluminium foil and stored in a desiccator at room temperature in a dark place for further evaluation studies. To determine different variables, batches of cast films were prepared. The compositions of films are given in (Table -1).

Evaluation of the films

Periodontal films were evaluated for physical characteristics as follows[17-19]-

Scanning electron microscopy

A Scanning electron microscope was used to study the surface characteristics of the films before and after dissolution. Samples were coated for 90 sec with gold palladium in a sputter coater (Structure Probe Inc) for a coating thickness of approximately 23.0 nm. Samples were stored in a dessicator until imaged on a field emission scanning electron microscope at 5.0 kV with a working distance of 8 to 10 mm. SEMs were taken at 5000X magnification and shown in (Figure 5 – 8).

Thickness of the films

Thickness of the film was measured using digital screw gauge (Mitutoyo) at different areas of the film and the average was calculated.

Uniformity of weight of the films

Film (size of 10x6 mm) was taken from different areas of film. The weight variation of each film was calculated.

Surface pH

Periodontal films were left to swell for 1 hour on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed double distilled water with constant stirring and poured into the petridish to solidify at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen film. The mean of three readings was recorded.

Folding endurance

The folding endurance of the films was determined by repeatedly folding the film at the same place till it broke or folded, which is considered satisfactory to reveal good film properties. This test was carried out on all the films.

Drug content uniformity of films

Content uniformity was determined by taking previously weighed film in a clean volumetric flask and warm buffer solution (37^0C) was added in small portions. The flask was kept in the shaker for 4 hours and then the final volume was adjusted to 100 ml with the buffer. The flask was kept undisturbed for one hour and 5 ml of the supernatant portion was taken in a 25 ml volumetric flask and diluted to 5 times in buffer. The turbid solution was centrifuged and the absorbance was read at absorption maximum 284 nm. on an U.V. spectrophotometer.

Moisture Loss

The 20 films of different concentrations are weighed accurately and then they are kept in desiccators for 3 days and then reweighed and by using the formula % moisture loss was calculated.

In-vitro study

The pH of gingival fluid lies between 6.5 – 6.8, phosphate buffer pH 6.8 was used as simulated gingival fluid. Also, since the film should be immobile in the periodontal pocket, a static dissolution model was adopted for the dissolution studies. Films of known weight were placed separately in small test tubes sealed with aluminium foil containing 1.0 ml of phosphate buffer (pH 6.8) and kept at 37 ^{0}C. The temperature was maintained at 37 ^{0}C by keeping the beaker on a magnetic stirrer with temperature control. The buffer was then drained off at the interval of 2 hours and replaced with a fresh 1.0 ml of buffer.

The concentration of drug was determined by UV spectrophotometer (shimadzu 1700) at 284 nm the procedure was continued for 48 hours. Studies were performed and the mean cumulative percentage of drug was calculated and plotted against time as shown in (Figure 9 and Table 3).

In-vitro drug release kinetics studies

In-vitro drug release has been recognized as an important element in formulation development. Several theories/kinetics models describe drug release from immediate and modified release dosage form. The quantitative interpretation of values obtained in the drug release study is facilitated by the use of a generic equation that mathematically translate the drug release curve in function of some parameter related with pharmaceutical dosage form . Many authors describe the release rate process by simply comparing the correlation coefficient values of lines collected from graphical presentation of different mathematical models as shown in (Table 4). In order to determine the mechanism of drug release from films, the data were treated using following mathematical models-(Figure 10-15).

1. Zero order (cumulative percentage of drug released versus time)
2. First order (log cumulative % drug remaining vs. time)
3. Higuchi square root law (cumulative percentage of drug released vs square root of time)

In-vivo study

In-vivo study of optimized film formulation was performed on male white rabbits. This study was approved by the institutional animal ethical committee CPCSEA (Committee for the purpose of control and supervision of experiments on animal, government of India), vide approval no. BU/Pharm/IAEC/11 /005, dated 26/03/2012.

In-vivo drug release study

In vivo tests were performed on film formulation F6 chosen on the basis of the results of in vitro test. The films were placed on the buccal mucosa of the animal. A rectangular

piece of the film was introduced to the buccal cavity by finger and adhered to the lower side of the buccal cavity facing the gum. Eating and drinking was prohibited during the first 3 hours.

After application, saliva samples (1.0 mL) were collected periodically at each time point of the experiment. Saliva samples were centrifuged at 5,000 rpm for 10 min to separate any solid components.The supernatant was transferred to centrifuge tubes and The tubes were vortex mixed with phosphate buffer 6.8 for 2 min and centrifuged at 13,000 rpm for 10 min. The supernatant is taken and add phosphate buffer 6.8 and analysed with the UV spectrophotometer for drug content(Table 5,6 and Figure 16).

Stability studies

Stability study was carried out to investigate the degradation of drug from formulation during storage.studies were performed on all periodontal films. The selected film of lomefloxacin were sealed in aluminium foil packaging and were stored in humidity chamber at accelerated (45 ± 2 ^{0}C, 75 ± 5% RH) and ambient (25 ± 2^{0}C, 60 ± 5% RH) condition for 30 days. Changes in the appearance and drug content of the stored films were evaluated at an interval of one week after storage. The data obtained were the mean of three determinations. The drug content data obtained showed that the content did not differ from the initial drug content by more than 5%.

Table 1: Formulation chart

S. No.	Ingredients	Formulation batch					
		F1	F2	F3	F4	F5	F6
1.	Lomefloxacin Hcl (mg)	200	200	200	200	200	200
2.	Ethyl cellulose 7std (mg)	200	400	600	-	-	-
3.	Ethyl cellulose 10std (mg)	-	-	-	200	400	600
4.	DBP % v/w of polymer wt.	10	-	10	10	-	10
5.	PEG400 % v/w of polymer wt.	10	10	-	-	10	-
6.	Chloroform (ml)	5	5	5	5	5	5

Table 2: Physicochemical characteristics of periodontal films containing lomefloxacin HCl

S. No.	Films	Thickness	Weight uniformity (mg)	Content uniformity %	Surface pH	Folding endurance	Moisture loss %
1.	F1	0.22±0.02	7.33±0.2	93±0.18	7	90±7.23	9.8±1.28
2.	F2	0.23±0.03	10.66±0.1	92±0.16	6.6	112±8.45	7.2±1.42
3.	F3	0.22±0.04	14.33±0.3	94±0.21	6.5	115±8.68	8.5±0.82
4.	F4	0.25±0.03	7.35±0.2	90±0.18	7	95±8.12	9.6±0.63
5.	F5	0.24±0.05	10.69±0.2	95±0.22	6.5	116±9.32	9.3±1.32
6.	F6	0.24±0.03	14.40±0.3	96±0.19	6.6	120±9.43	8.7±1.67

Table 3: In-vitro release profile of films from F1 to F6

S. No.	Time (hr)	Cumulative % Drug Release					
		F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	2	8.75	7.33	10.79	13.75	9.96	11.03
3.	4	12.15	15.05	15.88	18.15	15.53	17.86
4.	6	15.32	20.32	24.34	23.51	27.23	28.36
5.	8	18.64	32.24	43.29	26.42	39.4	45.03
6.	10	22.12	40.77	52.38	29.78	42.09	56.97
7.	20	29.90	57.85	67.45	33.21	61.17	69.24
8.	28	31.88	62.01	71.3	41.34	66.23	74.32
9.	34	38.54	68.36	75.03	45.66	75.88	77.76
10.	44	44.38	75.34	79.23	50.54	80.03	83.57
11.	48	46.59	78.34	83.21	52.74	84.28	86.31

Table 4: Kinetic models treatment of in-vitro drug release

S. No.	Formulation	Zero order	First order	Higuchi
		r^2	r^2	r^2
1.	F1	0.9367	0.9682	0.9981
2.	F2	0.8991	0.9779	0.9866
3.	F3	0.8934	0.9421	0.9824
4.	F4	0.8785	0.9386	0.9881
5.	F5	0.8934	0.9832	0.9837
6.	F6	0.8195	0.9536	0.9721

Table 5: Salivary drug concentration study of formulation F6 in animal model

S. No.	Time (hour)	Concentration (µg/ml)
1.	0	0
2.	0.5	0.38±0.03
3.	1	1.15±0.04
4.	2	1.97±0.06
5.	3	3.2±0.05
6.	6	2.9±0.06
7.	10	2.7±0.03
8.	20	2.4±0.05
9.	28	2.3±0.04
10.	34	1.8±0.03
11.	44	1.2±0.03
12.	48	0.23±0.04

Table 6: Pharmacokinetic parameter of lomefloxacin loaded formulation

S.No.	Parameters	Observation
1.	C_{max} (µm/ml)	3.2±0.05
2.	T_{max} (hrs.)	3
3.	AUC_{0-48} (µm/ml*h)	80.73

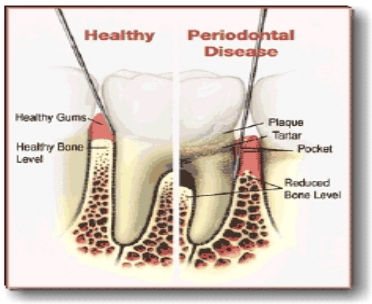

Figure 1: Comparison of a healthy tooth and periodontal diseased tooth[5]

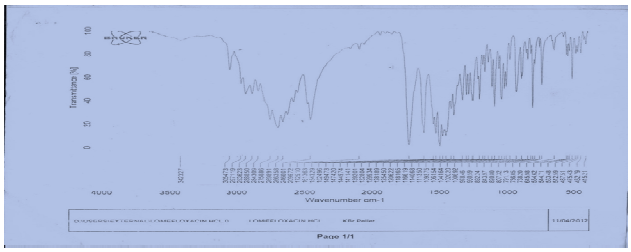

Figure 2: FTIR spectra of lomefloxacin hydrochloride

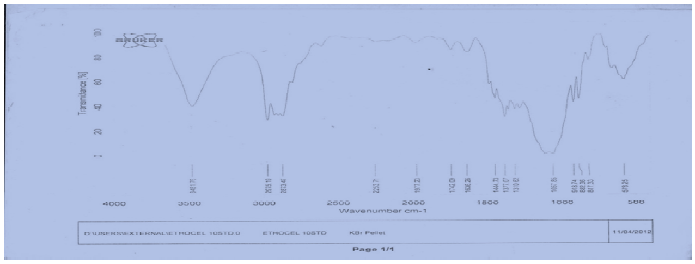

Figure 3: FTIR spectra of ethyl cellulose.

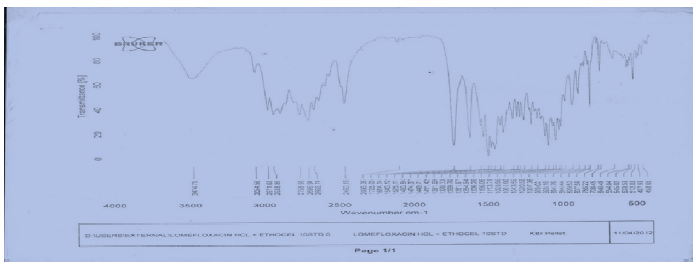

Figure 4: FTIR spectra of lomefloxacin hydrochloride with ethyl cellulose

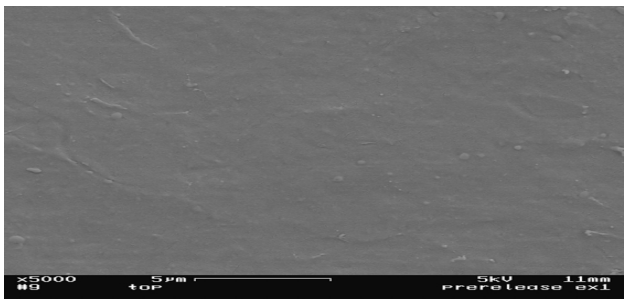

Figure 5: SEM of top surface of film before dissolution.

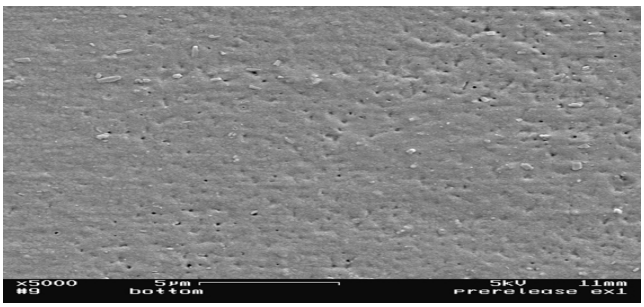

Figure 6: SEM of bottom surface of film before dissolution.

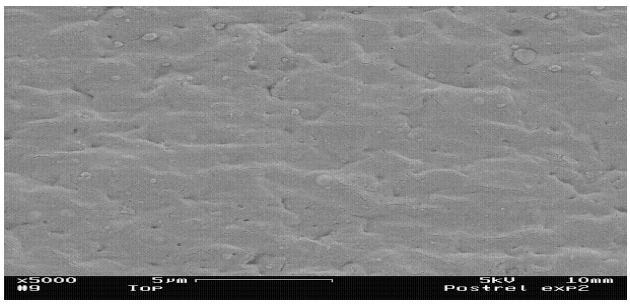

Figure 7: SEM of top surface of film after dissolution.

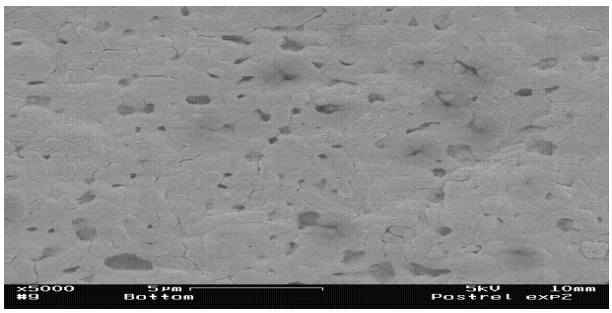

Figure 8: SEM of bottom surface of film after dissolution.

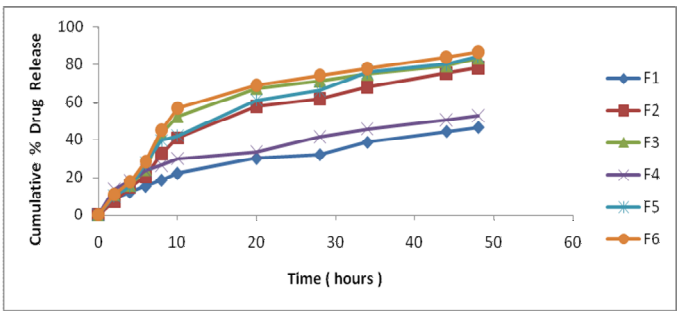

Figure 9: Comparative cumulative % drug release graph of formulations F1 to F6.

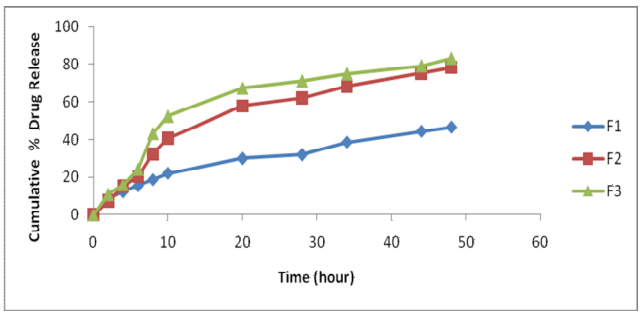

Figure 10: Zero order kinetic of F1 to F3

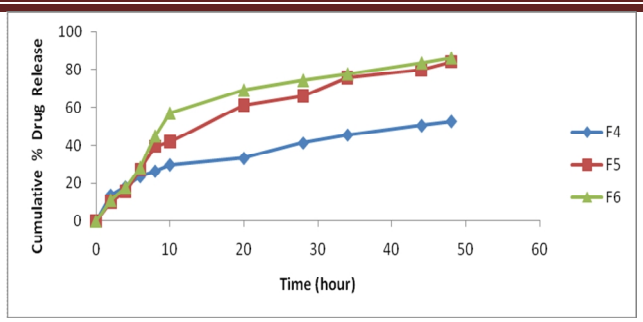

Figure 11: Zero order kinetic of F4 to F6

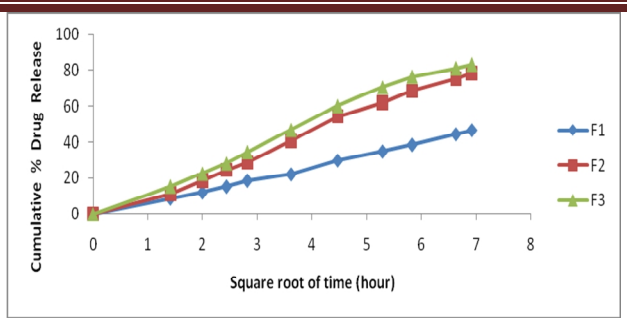

Figure 14: Higuchi model kinetic of F1 to F3

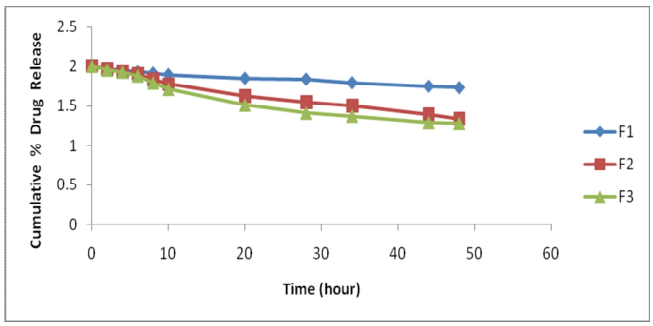

Figure 12: First order kinetic of F1 to F3

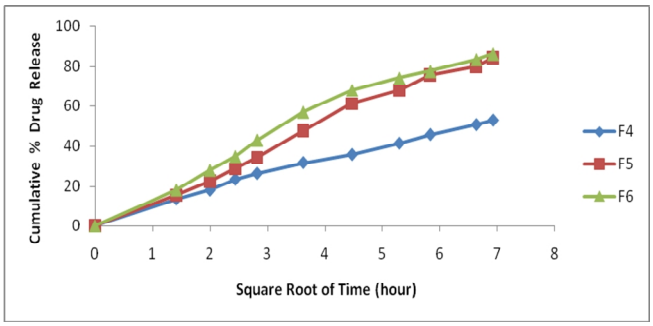

Figure 15: Higuchi model kinetic of F4 to F6

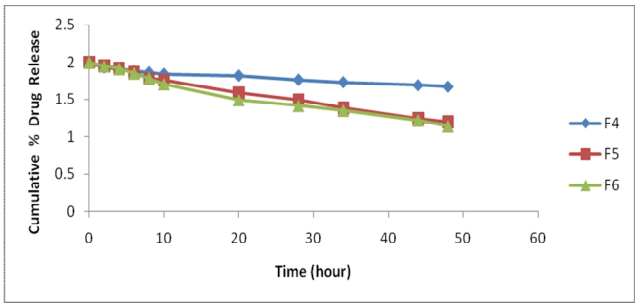

Figure 13: First order kinetic of F4 to F6

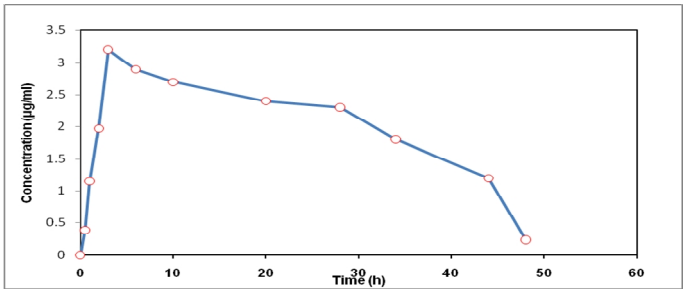

Figure 16: Salivary drug concentration - time profile of formulation F6

RESULT AND DISCUSSION

The possible interaction between drug and polymers were studies by FTIR spectroscopy. It was clear that there were no significant differences in IR peaks of drug alone and drug with polymer. Evaluation was done by different parameters with the help of different instruments and decide the optimize formulation. The film showed uniform thickness throughout, in the range of 0.22-0.24 mm. All formulations showed weight throughout in the range of 7.33 mg to 14.40 mg. The drug content in the dental films was within the limit of 92±0.16 to 96±0.19 %. The surface pH was measured by means of pH paper placed on the surface of the swollen film and was found to be 6.5 – 7 pH. The folding endurance was found to be 90-120. Moisture loss was found in the range of 7.2±1.42 % to 9.8±1.28%.

The cumulative percent drug release data from various formulations of films were found in the range of 46.59 % to 86.31 % . Highest percentage of drug release 86.31 % was observed from the film formulation F6. The slowest release was obtained from films containing the highest ratio of polymer. This result could be attributed to the higher viscosity of the polymer solution used in this formulation.

The release profile showed that there was rapid initial release of the drug because of the burst effect, due to elution of the drugs from the upper surface of the films. Once the burst effect was completed, slow and sustained release was seen up to the 48 hours. The drug release data were explored for the type of release mechanism followed. The 'r' values of the linear regressions for Higuchi plots were found to be higher, indicating that the data fits the Higuchi model well and the drug release was found to be predominantly controlled by diffusion process.

The in-vivo study of selected film formulations was carried out by means of salivary drug concentration measurement. Pharmacokinetics of the drug and its action on target pathogens, C_{max} was calculated. The calculated C_{max}, T_{max} and area under the salivary drug concentration curve (AUC_{0-48}) were observed 3.2±0.05 µm/ml, 3 hours and 80.73 µm/ml*h respectively. In the study, lomefloxacin hydrochloride films were successfully prepared using ethyl cellulose as the rate controlling polymer. These films were able to sustain the release of drug for long time**.**

CONCLUSION

In the present study, the aim of developing sustained release device of lomefloxacin hydrochloride was fulfilled. The delivery device provide initial high release and moderate release on the later time in in-vitro study. The developed film was satisfactory in terms of drug release.

The local delivery of antimicrobials into the periodontal pocket has opened up a new arena for the management of periodontal diseases. This type of drug delivery devices is likely to be well received by dental profession in future because it can produce much higher levels of drug at the site of interest with no side effects in comparison to conventional oral therapy for prolonged periods.

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REFERENCES

1. Haffajee A.D., Socransky S.S., Microbial etiological agents of destructive periodontal disease, Periodontology 2000 (1994) 78- 111.
2. http://www.dentalgentlecare.com/gum_disease.htm
3. Barnett ML. The oral-systemic disease connection. An update for the practicing dentist. J Am Dent Assoc. 2006;137 Suppl:5S-6S.
4. Williams RC. Understanding and managing periodontal diseases: a notable past, a promising future. J Periodontol. 2008;79(8 Suppl):1552-9.
5. Miller WD. The Micro-Organisms of the Human Mouth: The Local and General Diseases which Are Caused by Them. Philadelphia: SS White; 1880:274-342
6. Ahuja A.,Khar R.K., Ali J., Mucoadhesive drug delivery systems, Drug Development and Industrial Pharmacy 23 (1997) 489.
7. Roskos KV, Fritzinger BK, Armitage GC, Heller, Development of a drug delivery system for the treatment of periodontal disease based on bio erodible poly (orthoester). Biomaterials 1995;16:313-317.
8. Addy M., Renton - Harper P., Local and systemic chemotherapy in the management of periodontal disease: an opinion and review of the concept, J.Oral Rehab. 23 (1996) 219±231.
9. Stabholz A.,Sela M.N.,Friedman M., Golomb G, Solskolne A, Clinical and microbiological effects of sustained release chlorhexidine in periodontal pockets, J. Clin. Periodontol.13 (1986) 783±788.
10. Goffin G., Efficacy of a sustained local delivery of chlorhexidine Periochip as an adjunct to scaling and root planning in the treatment of chronic periodontal disease, Int. Dent. Rev. (1998) 1±18
11. Lachman L., Lieberman HA., Kanig JL., The theory and practice of industrial pharmacy. Verghese publishing house, third edition 1987: 171 195.
12. David G. Watson, "Pharmaceutical Analysis, A Textbook For Pharmacy Students And Pharmaceutical Chemistry," Published By Harcourt Publishers Limited, 1999:75-98.
13. Pavia D.L., Lampman G.M., Kriz G.S., "Introduction To Spectroscopy" Third Edition Printed In USA,1987: 353-78.
14. Robinson JR. and Lee VH., Controlled Drug Delivery: Fundamentals and Applications. Marcel Dekker Inc., New York, 1987: 7-9.
15. Morrision R.T. & Boyd R.N., "Organic Chemistry," Published by Prentice Hall of India Pvt. Ltd. New Delhi,Sixth Edition,2002:590-99.
16. Noha AN, Nabila AB, Fatima A, Ismail Lobna MM. Design & characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. Acta Pharm 2003; 53:199-212.
17. Khanna R, Agrawal SP, Ahuja A. Preparation and evaluation of buccal films of Clotrimazole for oral Candida infections. Indian J Pharm Sci 1997;59:299- 305.
18. Brahmankar DM., Jaiswal SB., Biopharmaceutics and Pharmacokinetics. A Teatise. Vallabh Prakashan, Delhi1, 995, 335-371.
19. Mastiholimath VS, Dandagi PM, Gadad AP, Patil MB,Manvi FV and Chandur VK. Formulation and evaluation of ornidazole dental implants for periodontitis. Indian J Pharm sci 2006; 68(1): 68-71.

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