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FORMULATION AND EVALUATION OF GEMIFLOXACIN INTRA-POCKET FILM FOR PERIODONTITIS

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ABSTRACT

In the present investigation, an effort was made to design a novel drug delivery system for the treatment of chronic periodontitis for site-specific delivery of Gemifloxacine mesylate which has excellent activity against wide range of microorganisms. The main purpose of formulating intra-pocket films using blend of chitosan and hydroxypropyl methyl cellulose was to extend drug release for prolonged period of time and to minimize frequent dosing of drug which would lead to better patient compliance. FTIR and UV spectroscopic methods revealed that there is no significant interaction between Gemifloxacine mesylate and polymers. The films were then evaluated for various parameters like thickness, folding endurance, weight variation, content uniformity, stability study and *in- vitro* drug release study. Formulation MG1 was the best chosen one concerning its high % of drug release 96.18 and retarded drug release as expected from its long $T_{50\%}$ = 4.97 days which is considered a promising tool in the treatment of periodontitis.

KEYWORDS: Gemifloxacine mesylate, intra-pocket, periodontitis, chitosan, hydroxypropyl methyl cellulose.

INTRODUCTION

Periodontal disease is a general term which includes several pathological conditions affecting the tooth supporting structures and mainly includes chronic periodontitis and aggressive periodontitis.[1] Periodontal disease is a result of local bacterial infection with apathogenic microflora within the periodontal pocket. The microflora found in periodontitis is complex and composed mainly of gram-negative anaerobic bacteria.[2]

Scaling and root planning (SRP) remains the 'gold standard' as the non-surgical treatment of chronic periodontitis. SRP may, however, fail to reduce or eliminate the anaerobic infection at the base of the pocket, within the gingival tissue or in furcations which in turn may serve as reservoirs for periodontopathic bacteria from which re-colonization of treated root surfaces can occur. The bacterial reservoir which is inaccessible for by mechanical debridement alone can be further eliminated with the adjunctive use of chemotherapeutic agents.[3]

Locally delivered antimicrobial therapy, in particular, has gained much interest because of the site-specific nature of periodontal infections, the higher concentration of anti-microbial agent delivered subgingivally and reduced side effects of systemic antibiotic use.[4]

Two particular problems common to many periodontal drug delivery systems are short retention time and difficult as well as time consuming application.[5,6] Gemifloxacin Mesylate is a synthetic broad-spectrum antibacterial agent for oral administration related to the fourth generation of fluoroquinolone class of antibiotics that has a broad spectrum of activity against Gram-positive and Gram-negative periodontopathic bacteria.[7,8] Species variability was evident: Porphyromonas gingivalis and Prevotella spp. were susceptible to 0.5 mg/L of Gemifloxacin Mesylate. These data suggest that GM may have a clinical role in the treatment of certain dental infections including chronic periodontitis.[9] Gemifloxacin is available as the Mesylate salt in the sesquihydrate form.[10] Gemifloxacin Mesylate in the form of conventional dosage form such as tablets and capsules is available for the treatment of bacterial infection in a dose of 320 mg daily.[11] Limited studies have been carried out to examine the role of local Gemifloxacin Mesylate formulated with rate controlling polymers in the management of chronic periodontitis although of its proved topical activity.[12]

MATERIALS AND METHOD

Materials

Gemifloxacin Mesylate was kindly supplied from (Hikma Pharmaceutical Co, Cairo, Egypt), Chitosan and hydroxypropyl methyl cellulose (HPMC) LV50 was purchased from (Sigma Aldrich, USA), Glycerol, Sodium hydroxide and Dipotassium hydrogen orthophosphate were purchased from (El-Nasr Pharmaceutical Chemicals Co, Cairo, Egypt).

Investigation of physicochemical compatibility of Gemifloxacin Mesylate and the polymers

The physicochemical compatibility between Gemifloxacin Mesylate and polymers was studied using Fourier transform-infrared (Maltson, Genesis II FTIR, USA). The FTIR spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}. The spectra of Gemifloxacin Mesylate alone and physical mixtures (1:1 w/w) of the drug with Chitosan and HPMC LV50 were compared with each other.

Construction of calibration curve of Gemifloxacin Mesylate in simulated saliva (pH 6.8) and determination of procedural constant

First derivative measurements of serial dilution of Gemifloxacin Mesylate in simulated saliva (pH 6.8) of 4, 6, 8, 10, 12, 14 and 16 µg/ml were carried out at wave length 258 nm, $\Delta\lambda = 4$ and scaling factor 10. To construct calibration curve, the reading of each sample was plotted against the corresponding concentration and the procedural constant (K) was calculated. All other formulations ingredients were separately dissolved in simulated saliva (pH 6.8) at the used concentrations and were measured at this specified wave length to test if the excipients exhibited any interference with the drug at the selected wave length.

Preparation of Gemifloxacin Mesylate periodontal films containing different concentrations of polymeric materials and glycerol as a plasticizer.

Selected films containing 0.4% w/w Gemifloxacin Mesylate were prepared by solvent casting technique. Glass Petri dishes were used for casting of the films. The weighed quantity of each polymer (Chitosan and HPMC) was gradually added to the required amount of distilled water (containing 1% v/v acetic acid in case of Chitosan) glycerol was added as plasticizer 10% (w/w) of the polymeric weight with constant stirring over night using a magnetic stirrer and the volume was adjusted.[13] The resulting solutions were filtered through sintered glass filter to remove the extraneous matter. Exactly 15 ml of the solution was poured and casted into petri dishes (9 cm in diameter) and kept overnight in closed condition to remove the entrapped air bubbles and drying in an oven at 40^{o}C. Casted films were carefully peeled off from the petri dishes after complete evaporation of solvent and then cut into pieces (7 X 2 mm) with a sharp razor blade. The films wrapped in an aluminum foil and stored in a desiccator at room temperature.[14] Formulations were coded from MG1 to MG10.The detailed compositions of medicated films are illustrated in Table (1).

Table (1): Composition of Gemifloxacin Mesylate intra-pocket films containing different concentrations of polymeric materials and glycerol as a plasticizer.

Components	Formulation code									
	MG1	MG2	MG3	MG4	MG5	MG6	MG7	MG8	MG9	MG10
Gemifloxacine Mesylate (mg)	400	400	400	400	400	400	400	400	400	400
Chitosan(gm)	1	2	3	1	1	0.75	-	-	-	-
HPMC(gm)	-	-	-	1	0.75	1	1	2	3	4
Glycerol (gm)	0.1	0.2	0.3	0.2	0.175	0.175	0.1	0.2	0.3	0.4
purified water to(gm)	100	100	100	100	100	100	100	100	100	100

Visual inspection and surface texture

The prepared Gemifloxacin Mesylate films were tested visually for their physical appearance, clarity, elegance, continuity, texture, absence of air bubbles, ease of removal or stickiness to petri dishes, cracks, flexibility and freedom of imperfections.

Drug content uniformity

The drug loaded Chitosan films of known weight of (7 X 2 mm) dimension were dissolved in 10 ml of 1% acetic acid and shaken until it dissolved. The drug solution was suitably diluted with simulated saliva (pH 6.8) and absorbance was measured.[15] In case of HPMC films, distilled water was used to dissolve the film.[16] And then suitably diluted with simulated saliva (pH 6.8).

Thickness uniformity

The thickness of each film was measured using micrometer screw gauge at different positions of the film and the average was calculated from five different spots of the film (n=5).

Uniformity of weight

Film pieces (7 X 2 mm) were taken from different areas of film and weighed individually using digital balance. The average weight of each film was calculated (n=3).[17]

Surface pH

The surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the periodontal mucosa. The film to be tested was placed in a petri dish and was moistened with 0.5 ml of distilled water. The surface pH was noted after bringing a pH paper near the surface of the film and allowing equilibration for 1 min**.** A mean of three reading was calculated**.**[18]

Folding endurance studies

The folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The film was folded number of times at the same place without breaking gave the value of the folding endurance. This test was done on all the films for six times.[19]

Estimation of percentage moisture loss

This test is of great significance as variation in moisture content causes a significant variation in the mechanical properties of the film. The capacity of the film to give away water is an important intrinsic parameter of the polymeric system in consideration to the release of drug. The percentage moisture loss test was carried out to check physical stability or integrity of the films. Six films of different concentrations of size (7 X 2 mm) were weighed accurately and then they were kept in a desiccator for 3 consecutive days and then reweighed.[20]

Percentage moisture loss was calculated by formula.

Percentage Moisture loss = (initial wt – final wt) / (initial wt) ×100.

***In vitro* drug release**

The pH of gingival fluid lies between 6.5 and 6.8. Simulated saliva (pH 6.8) was used. Since the film should be immobile in the periodontal pocket, a static dissolution method was adopted for the dissolution studies. Films (2 X 7 mm) were placed separately in small test tubes sealed with aluminum foil containing 1 ml Simulated saliva (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 drained off at specific interval of and replaced with a fresh 1 ml of Simulated saliva (pH 6.8).[21] The concentration of drug was determined spectrophotometrically. The cumulative percentage of drug released was plotted against time and release parameters were calculated to compare between investigated formulations. The release studies were performed in triplicates.

Stability study

The stability of the drug loaded films was studied at different temperatures using the reported procedure. The 3 films of size (2 X 7 mm) were weighed. The films were wrapped in aluminum foil and placed in petridishes. These containers were stored at ambient humid conditions, at room temperature (27 ± 2°C), oven temperature (40 ± 2°C) and in refrigerator

(5-8°C) for a period of 3 months. The samples were analyzed for physical changes such as color and texture. The drug content was estimated at an interval of 1 month using the procedures reported earlier.[22]

RESULTS AND DISCUSSION

Investigation of physicochemical compatibility of Gemifloxacin Mesylate and the polymers

IR spectra of the intact drug shows a broad band at 3410 cm^{-1} indicating the stretching of O-H carboxylic group , it shows also C-H aliphatic group stretching at 2900 cm^{-1} and a strong band at 1670cm^{-1} for C=O aryl ketone group[23] as shown in Figure (1). After physical mixing of the drug with different polymers in ratio 1:1 as shown in Figures (2,3) It reveals no chemical interaction (incompatibility) between the drug and each polymer takes place, this fact is supported by distinct appearance of the O-H carboxylic group, C-H aliphatic group and C=O aryl ketone group.

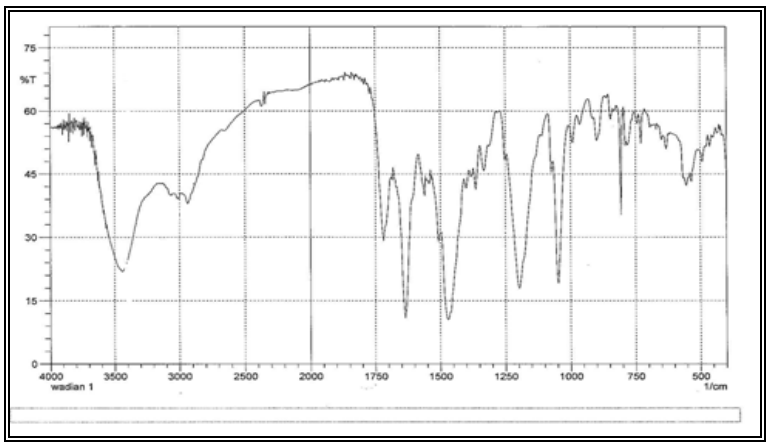

Fig. 1: IR Spectrum of Gemifloxacin Mesylate.

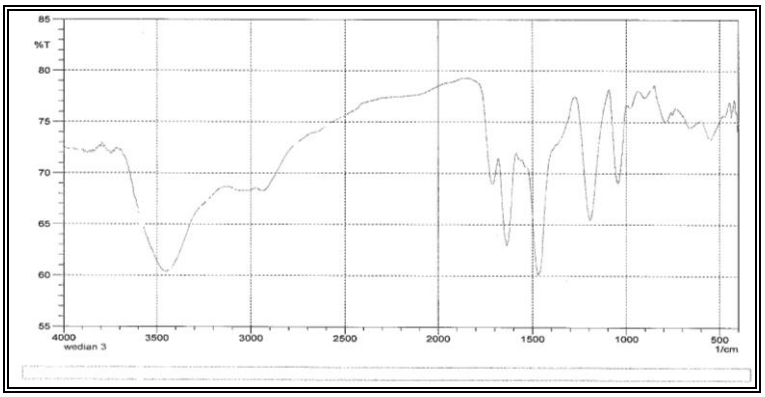

Fig. 2: IR Spectrum of Gemifloxacin Mesylate and Chitosan

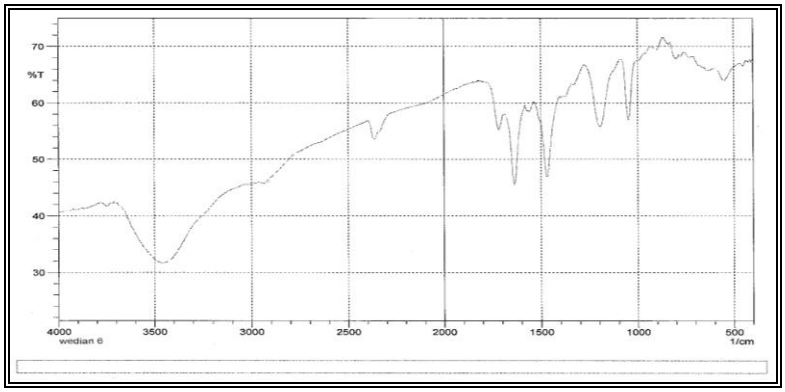

Fig. 3: IR Spectrum of Gemifloxacin Mesylate and HPMC

Construction of Standard calibration curve of Gemifloxacin Mesylate in simulated saliva (pH 6.8)

Figure (4) illustrate a linear relationship obeying Beer' s law between different concentrations and corresponding first derivative measurements of Gemifloxacin Mesylate dissolved in simulated saliva (pH 6.8) at wave length 258 nm, $\Delta\lambda$ =4 and scaling factor 10. Linearity is demonstrated by R^2 value of 0.9994, slope equals 0.0296 and the value of the procedural constant which is the reciprocal of the slope of the calibration curve equals 33.784.

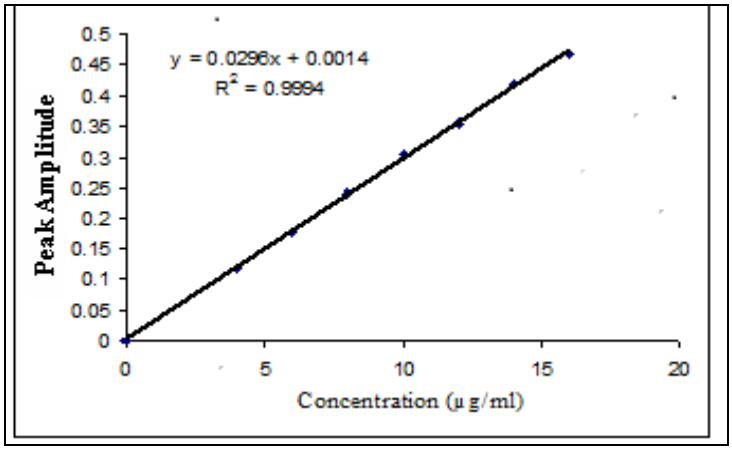

Fig. 4: standard calibration curve of Gemifloxacin Mesylate in simulated saliva (pH 6.8) at λ 258 nm Δλ= 4 and scaling factor 10.

Visual inspection and surface texture

Results of visual inspection showed that all Gemifloxacin Mesylate films were of accepted appearance and texture. They were homogenous, transparent, free from air bubbles and cracks, easily handled and easily removed from the petri dish.

Drug content uniformity

Results of drug content uniformity of periodontal films shown in Table (2).The results of drug content uniformity test indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 98.24 ± 0.002 % to 102.41 ± 0.002 %. Results indicated the efficiency of solvent casting method in preparing the GM films.

Thickness uniformity

Table (2) shows the results of thickness uniformity of periodontal films. All the films have uniform thickness and it was noted that the film thickness increased with the increase of the polymeric material concentration.[24] Films thickness ranged from 0.08 ± 0.07 to 0.14 ± 0.03 mm for Chitosan films, from 0.08 ± 0.09 to 0.1 ± 0.06 mm for Chitosan / HPMC films and from 0.08 ± 0.02 to 0.13 ± 0.02 mm for HPMC films.

Weight uniformity

Table (2) shows Results of weight uniformity of periodontal films. Periodontal films (2 X 7 mm) were tested for uniformity of weight. All the films have uniform weight and it was also noted that the film weight increased with the increase of the polymeric material concentration.[25] The average weight of the film ranged from 1.16 ± 0.05 to 1.71 ± 0.04 mg for Chitosan films, from 1.23 ± 0.08 to 1.42 ± 0.04 mg for Chitosan / HPMC films and from 1.29 ± 0.09 to1.86 ± 0.02 mg for HPMC films.

Surface pH

The surface pH of the film is an important factor. Irritation or inflammation to the mucosa may be induced if the film is highly acidic or alkaline.[26] Table (2) shows the values of surface pH of medicated periodontal films, it was noticed that, the surface pH values of Chitosan films ranged from 5.7 ± 0.02 to 6 ± 0.03, Chitosan / HPMC films ranged from 6 ± 0.16 to 6.2 ± 0.35 and HPMC films ranged from 6.1 ± 0.04 to 6.4 ± 0.23. As the pH range is close to the neutral pH, these films are suitable to be inserted into the periodontal pocket with no irritation to the mucosa.

Estimation of percentage moisture loss

The data presented in Table (2) reveals that percentage moisture loss of all formulations ranged from 6.25 ± 0.06 to 10.98 ± 0.08%. It also noticed that percentage moisture loss was least in Chitosan films. However, HPMC films exhibited highest loss, and for Chitosan / HPMC films the incorporation of the HPMC with Chitosan gave higher percentage moisture loss than Chitosan

alone.[27] Also it reveals that upon increasing the concentration of HPMC an increase in percentage moisture loss was occurred.[28]

Folding Endurance

Table (2) shows results of folding endurance of periodontal films. All formulations exhibited good folding endurance exceeding 300, indicating that they are tough and flexible.[29] The Chitosan films showed higher folding endurance values as it ranged from 360 ± 5 to 390 ± 1 as compared to the more hydrophilic HPMC films ranged from 305 ± 4 to 340 ± 6 due to less hydrophilic characteristics of Chitosan.[16]

Table (2): Weight, thickness measurements, percentage drug content, surface pH, percentage moisture loss and folding endurance of Gemifloxacin Mesylate intra-pocket films

Formulation code	Weight (mg) Mean ± SD	Thickness (mm) Mean ± SD	% Drug content Mean ± SD	Surface pH Mean ±SD	percentage Moisture Loss Mean ±SD	Folding Endurance Mean ±SD
MG1	1.16 ± 0.05	0.08 ± 0.07	98.24 ± 0.002	6 ± 0.03	6.25 ± 0.06	360 ± 5
MG2	1.37 ± 0.01	0.11 ± 0.04	99.63 ± 0.005	5.8 ± 0.01	7.18 ± 0.01	375 ± 2
MG3	1.71 ± 0.04	0.14 ± 0.03	100.21 ± 0.006	5.7 ± 0.02	8.23 ± 0.02	390 ± 1
MG4	1.42 ± 0.04	0.09 ± 0.05	98.76 ± 0.008	6.1 ± 0.24	8.42 ± 0.05	352 ± 2
MG5	1.31 ± 0.06	0.1± 0.06	101.22 ± 0.006	6.2 ± 0.35	8.37 ± 0.11	358 ± 5
MG6	1.23 ± 0.08	0.08 ± 0.09	102.41 ± 0.002	6 ± 0.16	8.82 ± 0.04	347 ± 4
MG7	1.21 ± 0.03	0.08 ± 0.02	98.33 ± 0.001	6.1 ± 0.04	8.54 ± 0.03	340 ± 6
MG8	1.29 ± 0.09	0.09 ± 0.06	100.87 ± 0.009	6.3 ± 0.02	9.12 ± 0.22	335 ± 1
MG9	1.64 ± 0.06	0.11 ± 0.07	99.64 ± 0.007	6.4 ± 0.18	10.31 ± 0.07	329 ± 3
MG10	1.86 ± 0.02	0.13 ± 0.02	99.11 ± 0.010	6.4 ± 0.23	10.98 ± 0.08	305 ± 4

***In vitro* release of Gemifloxacin Mesylate from GM intra-pocket films**

The results of the in vitro release of Gemifloxacin Mesylate from intra-pocket films showed that they could be arranged descendingly according to the time required for maximum cumulative drug released as follows Chitosan films (9 days) > Chitosan / HPMC films (5 days) > HPMC films (3.5 days).

It was noted that MG1 (containing 1% Chitosan) shows the slowest release rate expressed as half time ($T_{50\%}$= 4.97days). While MG9 (containing HPMC 3%) shows the highest release rate ($T_{50\%}$ = 2.18days). The retardation of drug release from Chitosan films could be due its less hydrophilic nature while the faster release of HPMC films could be due to its more hydrophilic nature.

It was noted that the release of Gemifloxacin Mesylate from the formulations was according to Zero order kinetics.[30] Data can be arranged in descending order according to their K values as MG9 > MG8 > MG7 > MG10 > MG6 > MG4 > MG5 > MG3 > MG2 > MG1 (22.9, 22.64, 21.35, 21, 17.66, 17.22, 16.67, 10.58, 10.18 and 10.05% mg min^{-1}) .

It was noticed from rate and extent data that formulation MG2 was the best chosen one concerning its high % of drug release 96.18 and retarded drug release as expected from its long $T_{50\%}$ = 4.97 days so this formulation is selected for clinical evaluation.

Table (3): Kinetic parameters of Gemifloxacin Mesylate release data from different intra-pocket films according to Zero order, First order and Diffusion kinetics.

Formulation code	R^2			Release order	k %mg min^{-1}	$T_{50\%}$	n	K	Main transport mechanism
	Zero	First	Diffusion						
MG1	0.9986	0.9327	0.9950	Zero	10.05	4.97	0.859	0.1524	Diffusion and non-Fickian transport
MG2	0.9989	0.9719	0.9843	Zero	10.18	4.90	0.827	0.1364	Diffusion and non-Fickian transport
MG3	0.9994	0.9140	0.9871	Zero	10.58	4.72	1.03	0.0984	Super Case II transport
MG4	0.9957	0.9635	0.9900	Zero	17.27	2.89	0.718	0.2529	Diffusion and non-Fickian transport
MG5	0.9982	0.9666	0.9911	Zero	16.67	2.99	0.767	0.2387	Diffusion and non-Fickian transport
MG6	0.9912	0.9717	0.9889	Zero	17.66	2.83	0.663	0.2766	Diffusion and non-Fickian transport
MG7	0.9901	0.9324	0.9787	Zero	21.35	2.34	0.667	0.3382	Diffusion and non-Fickian transport
MG8	0.9846	0.9128	0.9667	Zero	22.64	2.20	0.784	0.2722	Diffusion and non-Fickian transport
MG9	0.9835	0.9218	0.9626	Zero	22.90	2.18	0.861	0.2360	Diffusion and non-Fickian transport
MG10	0.9746	0.9029	0.9559	Zero	21.00	2.38	0.954	0.2089	Diffusion and non-Fickian transport

Stability study

There were no significant changes in the appearance of the selected films and the drug content data obtained showed that the content didn't differ from the initial drug content by more than 5% so they were considered as stable formulations.

CONCLUSION

In the present research Gemifloxacin Mesylate intra-pocket films were developed with combination of chitosan and HPMC. By doing compatibility study, drug was found to be compatible with formulation excipients. The developed formulations showed satisfactory results for physical appearance, % drug content, thickness and weight measurements, percentage moisture loss, folding endurance, surface pH, stability and *in vitro drug release*. Formulation containing 1% w/w chitosan was considered the best formulation as it gives satisfactory *in vitro* result which is considered a good candidate for local delivery systems.

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