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Formulation and *in-vitro* evaluation of Bio-degradable polymer based Sparfloxacin Periodontal chip

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ABSTRACT

This study was designed to formulate and evaluate the *in vitro* drug release of biodegradable polymer based periodontal chip containing Sparfloxacin for the treatment of periodontitis by local administration. Biodegradable polymers namely Poly (lactic-co-glycolic acid) (50:50) and Polyvinyl pyrrolidone **(**PVP) were used in the formulation of the periodontal chip. The drug films were prepared by solvent casting method. The Periodontal chip was then evaluated for *in-vitro* drug release study for 21 days*. In vitro* drug release profile of periodontal chip 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 21 days of study. The study suggests that biodegradable polymer based periodontal chip of Sparfloxacin is a potential local drug delivery device for the treatment of periodontitis.

Keywords: Periodontitis, Sparfloxacin, PLGA (50:50), PVP, local drug delivery, in-vitro drug release.

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INTRODUCTION

Periodontitis is a dental disease, which is an inflammatory response to bacteriological infections [1]. Periodontitis destroys the attachment apparatus of teeth resulting in periodontal pocket formation and alteration of normal osseous anatomy. The primary objective of the therapy for patients with chronic periodontitis is to halt disease progression and to resolve inflammation. The scaling and root planning reduces probing depth, gain clinical attachment, inhibit disease progression and regenerates lost periodontal structures [2].

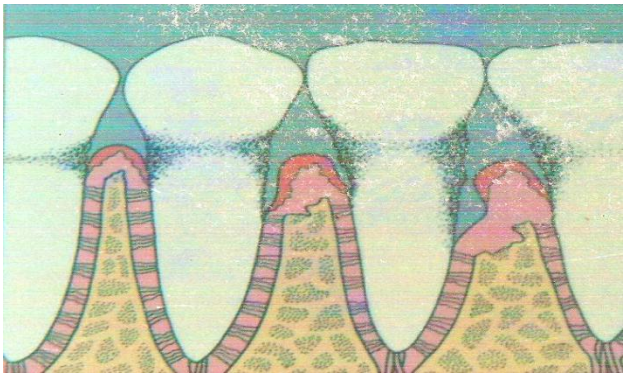

Fig: 1 The image shows the appearance of gingiva during periodontitis.

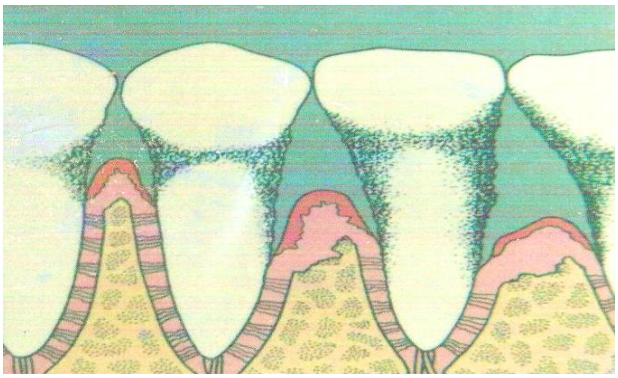

Fig: 2, The image shows the appearance of gingiva during advanced periodontitis.

Drugs especially antibiotic therapy is an adjunctive in the management of periodontitis in patients with advanced periodontitis [3]. Numerous investigations have assessed the progression of periodontitis to improve periodontal status. Potent risks associated with the systemic administration of antibiotics include development of resistant bacterial strains, emergence of opportunistic infections and possible allergic sensitization of patients. The prolonged use of non steroidal anti inflammatory drugs leads to harmful adverse effects such as gastrointestinal upset, hemorrhage, renal, hepatic impairment, central nervous system disturbances, inhibition of platelet aggregation, prolonged bleeding time, bone marrow damage so on.

Systemic antimicrobials such as adjuncts to mechanical therapy have had a positive effect on clinical as well as microbiological parameters [5]. But the impact of this approach is reduced by the fact that the antibiotic is normally difficult to maintain in therapeutic concentrations at the site over the course of the treatment period. Moreover, systemic antibiotic therapy carries with it the risk of the host developing resistance. Due to these negative effects, the use of local drug delivery devices containing antibiotics which can maintain therapeutic concentrations at the site of infection is an approach that may be explored. This could enhance the therapy of periodontal diseases while also reducing side effects [6]. The potential uses of local drug delivery devices are to enhance therapy at sites that do not respond to conventional treatment [4]. Ultimately the result of local drug delivery is evaluated with regard to the magnitude of improvement of disease severity.

In the present study the Sparfloxacin used for the formulation of periodontal chip as it have a number of advantages over other classes of antibacterial. Sparfloxacin is a broad spectrum anti-biotic, well absorbed orally, well distributed in tissues, have relatively long serum half-life, minimal toxicity and deep tissue or cell penetration. It is a new fluoroquinoline anti-biotic which has a higher potency against gram positive bacteria and anaerobes than other fluoroquinolines.

PLGA [poly (lactic-*co*-glycolic acid)] is a copolymer which is used in a host of Food and Drug Administration (FDA) approved therapeutic devices, owing to its biodegradability and biocompatibility. PLGA is synthesized by means of random ring-opening co-polymerization of two different monomers, the cyclic dimers (1, 4-dioxane-2, 5-diones) of glycolic acid and lactic acid [11]. PLGA has been successful as a biodegradable polymer because it undergoes hydrolysis in the body to produce the original monomers, lactic acid and glycolic acid. In normal physiological condition, lactic acid and glycolic acid are metabolic products of various metabolic pathways in the body. Since the body effectively deals with the two monomers, there is very minimal systemic toxicity associated with using PLGA for drug delivery or biomedical applications. In the present study Polyvinylpyrrolidone (PVP) was also used since it was soluble in water and other polar solvents, when dry it is a light flaky powder, readily absorbs up to 40% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings. PVP was initially used as a blood plasma substitute and later in a wide variety of applications in medicine, pharmacy, cosmetics and industrial production [7]. PVP is also used in personal care product like toothpastes and has also been used in contact lens solutions [8, 9]. The U.S. Food and Drug Administration (FDA) has approved this chemical for many uses, [10] and it is generally considered as safe material.

The proper design of an *in-vitro* drug elution system permits accurate evaluation and mechanistic analysis of the sustained release profiles of an intra-pocket device. The periodontal pocket is poorly perfused, and the volume of fluid present in the pocket is very small. In order to simulate condition prevailing in an inflamated gingival cavity, a new *in-vitro* drug release pattern was developed by our research group [2]. The *in-vitro* drug release study was carried

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out at pH 7.8 since pH of gingival crevicular fluid is between 7.5 to 8.0 and the flow of fluid at an individual site is 150-200 µg/m L which amounts to about 5mL per day.

MATERIALS AND METHODS

In the present study Sparfloxacin was given as a gift sample from Dr. Reddy's Laboratory, Hyderabad, India. Poly (lactic-co-glycolic acid) (50:50) was bought from Boehringer Ingelheim Pharma GmbH & Co Germany. Polyvinylpyrrolidone **(**PVP) was bought from Nice Chemicals, Kochi. Diethyl phthalate was bought from Nice Chemicals, Kochi. Methylene chloride was bought from SD Fine-Chem, Ltd, Mumbai.

Formulation of periodontal chip[2]

The biodegradable polymer based Sparfloxacin film was formulated as per the method discussed below. Biodegradable polymers PLGA 50:50 and PVP were weighed accurately and dissolved in methylene chloride in a 100 ml glass beaker. Stirring was carried out using a magnetic stirrer at 300 rpm and to this accurately weighed Sparfloxacin was transferred. Stirring was continued until a homogenous mixture of polymer and drug in solvent was achieved. The required amount of plasticizer diethyl phthalate was also added into the polymer and drug mixture.

To cast the film a petridish of 7.5cm was used on which a glass ring of diameter 36mm and thickness 0.5mm was placed. The homogeneous mixture was poured into the glass ring in the petridish and covered with a wide mouthed glass funnel to achieve uniform evaporation of solvent at room temperature. After the solvent was evaporated the film was removed from the ring and cut into periodontal chips with dimensions of 5mm length, 2mm width and 0.25mm thickness. Periodontal chip was stored in air tight containers.

Standard graph

The standard graph of Sparfloxacin in methylene chloride was prepared by dissolving accurately weighed quantities in serial dilutions of different known concentrations. The absorbance was measured at 289.5nm using SHIMADZU 160UV PC Spectrophotometer and the values were plotted to get a linear graph [2].

In-vitro evaluation

The chip of Sparfloxacin was placed in 10 mL vials. To these 5 mL of phosphate buffer pH 7.8 was transferred and tightly closed. The temperature was maintained at 37^{o} C by placing vial in an incubator. Every 24 hours the dissolution medium was taken out and replaced with fresh medium. The amount of drug released into the medium was determined by measuring the absorbance at 289.5 nm using UV Spectrophotometer after suitable dilutions. The in vitro study was done with five replicates for 21 days [2].

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RESULTS AND DISCUSSION

Table-1 Standard graph of Sparfloxacin

S. No	Concentration (µg/ml)	Absorbance 289.5nm
1	20	0.9414
2	40	1.8919
3	60	2.9250
4	80	3.9956

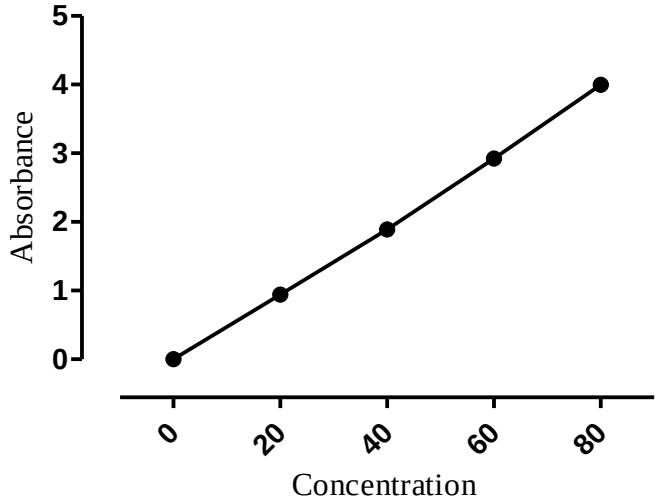

Fig: 3 Standard graph of Sparfloxacin absorbed at 289.5nm using SHIMADZU 160 UV PC Spectrophotometer.

The absorbance of the different serial dilutions prepared at different known concentrations was measured at 289.5nm using SHIMADZU 160UV PC Spectrophotometer and the values were shown in table no-1, and plotted to get a linear graph, Figure: 3.

Formulation of periodontal chip

Table -2 Ingredients used in the formulation of the periodontal chip of Sparfloxacin.

Amount of PLGA 50:50 (mg)	Amount of PVP (mg)	Diethyl phthalate (%)	Amount of Sparfloxacin (mg)	Film character
498.24	55.36	5	221.4	Good

The optimized formula for the formulation of the periodontal chip of Sparfloxacin was obtained by the trial and error method. The drug content to be present in the periodontal chip was expected to be 2mg so the drug amount is calculated accordingly and shown in table-2. The biodegradable polymers PLGA (50:50): PVP were taken at the ratio of 9:1 in this formulation and it produced good film.

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In-vitro evaluation

Table-3 The drug release profile of periodontal chip of PLGA (50:50): PVP based periodontal chip of Sparfloxacin

DAYS	DRUG RELEASE (µg)	CUMULATIVE DRUG RELEASE (µg)	CUMULATIVE DRUG RELEASE (%)
1	192	192	9.6
2	98	290	14.5
3	86	376	18.8
4	70	446	22.3
5	70	516	25.8
6	74	590	29.5
7	72	664	33.1
8	70	732	36.6
9	62	794	39.7
10	50	844	42.2
11	50	894	44.7
12	48	974	47.1
13	50	998	49.9
14	50	1048	52.4
15	46	1094	54.7
16	38	1132	56.6
17	32	1164	58.2
18	36	1200	60.0
19	26	1226	61.3
20	32	1258	62.9
21	34	1292	64.6

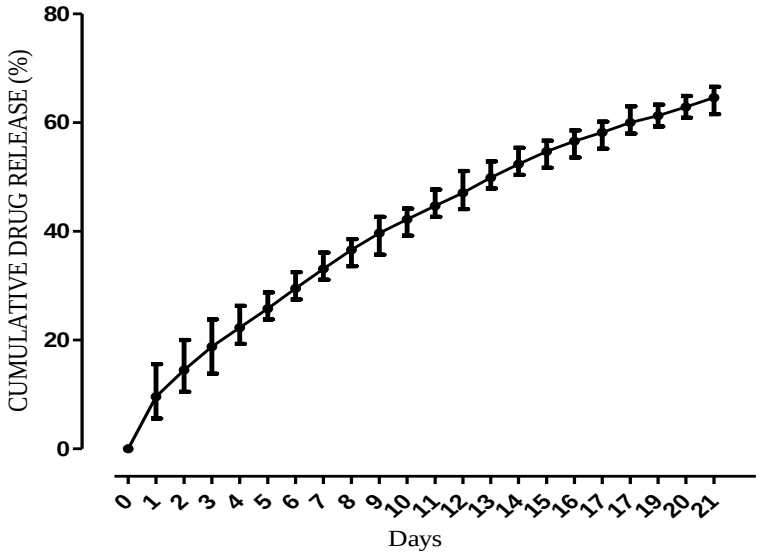

Figure-4, The *in-vitro* drug release profile of PLGA (50:50): PVP based periodontal chip of Sparfloxacin

The periodontal chips were placed in a vial of 10ml and placed in an incubator and the study was carried out for 21 days. The *in-vitro* drug release profile showed an initial burst of drug release of 192 µg of the drug Sparfloxacin on the first day i.e. 9.6%. The drug release on the 21st day was 34 µg, i.e. 64.6 % of the drug was released. From the results obtained we can clearly see that the drug release was above the minimum inhibitory concentration required by the periodontal pathogens and also sustained throughout the *in-vitro* drug release study. The results were tabulated in table-3.

CONCLUSION

The advantages of local intra-pocket delivery of the periodontal chip over systemic delivery in periodontitis are that administration is less time-consuming and a lower dose of drug is required to achieve effective therapeutic concentration at the site of action. In the present study only 2mg of the drug Sparfloxacin was used in the formulation of the periodontal chip, which is 100 times less than the drug administered through the systemic route. The periodontal film was flexible and possessed satisfactory physicochemical characteristics. The periodontal chip showed an initial burst release of drug and release was sustained for 21 days. The periodontal chip was formulated with biodegradable polymer so there is no need to remove the periodontal chip after the treatment. Treatment of Periodontitis with periodontal chip is cost-effective and will have good patient compliance as it is easy to use. So the biodegradable polymers PLGA (50:50) and PVP based periodontal chip will have a role in the therapy of periodontal chip.

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