

DESIGN, CHARACTERIZATION AND *IN VITRO* EVALUATION OF DENTAL IMPLANTS OF ACECLOFENAC SODIUM FOR PERIODONTITIS

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ABSTRACT

A Novel drug delivery system for the treatment of Periodontitis was developed for site specific delivery of Aceclofenac sodium which has excellent anti inflammatory activity. Dental Implants are pharmaceutical devices in the form of strip with very small drug loading capacity and it can be formulated in the size of 0.8 x 0.4 square cm. The objective of the present study was to formulate and evaluate controlled release dosage form of Aceclofenac sodium for the topical treatment of inflammation in periodontitis. It is a site specific delivery device with once daily continuous delivery of Aceclofenac sodium as an anti inflammatory compound with excellent activity against the Inflammation. Dental Implants was prepared by Solvent casting technique, using polymers like HPMC K 100 , HPMC K 4 M, Gelatin and Ethyl cellulose with Dibutyl phthalate as Plasticizer. The physicochemical parameters like Thickness, Weight variation, Content uniformity and *in vitro* Release studies were evaluated and the drug release was found to follows Non-Fickian diffusion mechanism. Formulation F2 shows 20.93 % of drug at the end of 12th hr and was considered as best formulation for further controlled release. The drug release data shows a best fit for korsermayer - Peppas fitting curve and obeys Zero order release kinetics.

Keywords: Aceclofenac sodium, Hydroxyl Propyl Methyl Cellulose (HPMC), Eudragit, Dental Implants.

INTRODUCTION

Periodontal diseases are infections affecting a significant proportion of people in all populations¹. Periodontal disease is a term that encompasses several pathological conditions affecting the tooth supporting structures. Periodontal disease includes conditions such as chronic periodontitis, aggressive periodontitis, systemic disease associated periodontitis, and necrotizing periodontitis². A site-specific system aims at delivering the therapeutic agent at sufficient levels inside the pocket and at the same time minimizing the side effects associated with systemic drug administration⁴. In conventional mode of drug administration, many drugs do not reach target areas in the body in sufficient concentration because of premature inactivation and excretion. The systemic drug administration has been useful in treating periodontitis but the disadvantage is that, drug is diluted several thousand folds before it reaches the site and exposes the drug to rest of the body parts leads to potential side effects. This problem can be overcome by administering the drug directly to the intended site of action with lesser dose³. The local production of prostaglandins and other metabolites of arachidonic acid within the periodontal tissues contribute to alveolar bone resorption in periodontitis. Research findings have shown that inhibitors of prostaglandin production, such as nonsteroidal anti-inflammatory drugs (NSAIDs), could affect the course of bone loss in periodontal disease⁵. Data from prospective animal experiments and human studies support this concept, and indicates that NSAIDs can reduce gingival inflammation and reduce alveolar bone resorption⁶. There is also evidence that systemic administration of antibiotics and NSAIDs are effective in altering the progression of certain forms of periodontitis⁷. Aceclofenac sodium has analgesic, antipyretic and anti-inflammatory activities. It is a non-selective cyclo-oxygenase inhibitor with potency greater than several other NSAIDs. Aceclofenac appears to reduce the intracellular concentration of free arachidonate in leucocytes, perhaps by altering the release or uptake of the fatty acid⁷. Sustained drug delivery systems are able to provide very precise control over drug release for a prolonged period of time eliminating the need for frequent dosing and minimizing side effects, thereby increasing patient compliance and comfort⁸.

MATERIALS AND METHODS

Aceclofenac sodium was obtained as gift sample from Milton labs Pvt. Ltd., Pondicherry., India. Ethyl cellulose, Hydroxy Propyl Methylcellulose (HPMC K100, K4M), Gelatin were obtained from Novel drugs Pvt. Ltd., Trichy, India. Dibutyl phthalate from GKM laboratories, Pondicherry., India. Other materials used in the study were of analytical grade.

Compatibility studies

Aceclofenac sodium and polymers were subjected to FT-IR studies. 3 mg of pure drug/ combination of drug-polymer were triturated with 97 mg of potassium bromide in a smooth mortar. The mixtures were placed in the sample holder and were analyzed by FT-IR to study the interference of polymers with the drug.

Preparation of Crosslinked Implant Films

Solvent casting technique

The required quantity of bees wax was weighed and melted in a beaker at around 70 – 80 ° c. The required quantity of polymer was added to molten bees wax and mixed well. Aceclofenac sodium was dispersed in the above solution. The content was equally distributed by pouring the solution gently on an ice cold tile then the mass was solidified by keep the content in freezer. After solidification, the mass was cut into pieces of equal sizes. The films were cross linked by exposure to glutaraldehyde. The chamber was previously saturated with the vapour of 2%v/v glutaraldehyde for 24 h. The films were exposed to the vapour for 2 and 4 h respectively and then dried. The dry films were cut into pieces, wrapped in aluminum foil and stored in calcium chloride desiccators for further evaluation.

Evaluation of Implants

Thickness uniformity of the films

Thickness of the film was measured using digital screw gauge at different areas of the film and the average was calculated. The thickness of three films (0.8 x 0.4 sq.cm.) from each batch was determined at six different points on the film and the mean calculated.

Weight variation

Individual weights of twenty films of the same size (0.8 x 0.4 sq.cm) were weighed on an electronic balance and the mean weight was calculated. The weight variation of each film was calculated.

Moisture content

Percent moisture loss was determined by keeping the film in a desiccator containing anhydrous calcium chloride. After three days, the films were taken out, re-weighed and the percent moisture loss was calculated using the formula:

$$\text{Moisture content (\%)} = (\text{Initial wt} - \text{Final wt}/\text{Initial wt}) \times 100$$

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 recorded⁹.

Viscosity

Aqueous solutions containing both polymers and plasticizers were prepared in the same concentration as that of films. Viscosity was measured at 20 rpm at room temperature using Brookfield viscometer. The recorded values were mean of five determinations.

Folding endurance

The folding endurance of the films was determined by repeatedly folding the film until it broke or folded, which was considered satisfactory to reveal good film properties. This test was carried out on all the batches of the films¹⁰.

Estimation of content uniformity

The drug-loaded films of known weight were dissolved in phosphate buffer pH 6.8 and left it for 24 hrs, the amount of drug present in the implant was estimated by UV/VIS spectrophotometer at 278 nm.

In vitro drug release studies

Since the pH of gingival fluid lies between 6.5 – 6.8, phosphate buffer pH 6.8 was used for release pattern. Since the film should be immobile in the periodontal pocket, a static dissolution model was adopted for the dissolution studies. Diffusion study was done in 400 ml phosphate buffer (pH 6.8) and kept at 37 ± 0.5 °C for 12 h. 5 ml sample taken at different time interval and replaced with a fresh 5.0 ml of buffer to maintain. The concentration of drug was determined by UV/VIS spectrophotometer at 278 nm. Following the *in vitro* release studies, the test films were further analyzed for unreleased drug by dissolving the films in aqueous acetic acid with suitable dilution. The amount of drug released into the dissolution medium plus residual drug content of the films were summed to obtain the actual drug content.¹¹

Release kinetics studies

To find out the mechanism of drug release from hydrophilic matrices, the dissolution data of tablets of each batch treated with different kinetics release equation¹⁸ Zero order: $Q = K_0 t$ (1); Higuchi's square root at time: $Q = K_H t^{1/2}$ (2) and Korsmeyer and Peppas: $M_t/M_\infty = KM t^n$ (3). Where Q is the amount of drug released at time t, M_t/M_∞ is the fraction of drug released at time t. K_0 is Zero order release rate constant. K_H is Higuchi's square root of time

kinetics drug release constant. KM is constant incorporating geometric and structural characteristic of tablets and 'n' are the diffusion exponent indicative of the release mechanism. In case of tablets (which are of cylindrical shape), a value of $n < 0.45$ indicates Fickian or Case I release; $0.45 < n < 0.89$ for non-Fickian or anomalous release; $n = 0.89$ for Case II release; and $n > 0.89$ indicates Super Case II release.

Stability studies

Three sets (12 strips in each set) of films (size: 0.8x0.4 sq.cm) were weighed. The films were wrapped individually in aluminium foil and placed in Petri dishes. These containers were stored in an oven (at 45 ± 2 °C/75%RH). The samples were analyzed for physical characteristics. Drug content was estimated at regular intervals as described earlier.¹²

RESULTS AND DISCUSSION

Sustained release dosage forms of Aceclofenac Dental Implants were prepared by Solvent casting technique. The compatibility study of drug and polymer was shown in Figure.1. Five different formulation using Polymers like HPMC K 100 , HPMC K 4 M, Gelatin and Ethyl cellulose with Dibutyl phthalate as Plasticizer was formulated and release studies was studied for 12 hrs. The formulation of dental implants was shown in Table.1. The prepared films were translucent and smooth surfaced with good tensile strength. The procedure developed to prepare the films was reproducible. All the formulations shows uniform thickness throughout the film in the range of 1.82 ± 0.02 to 1.98 ± 0.02 mm ($n = 3$). The implants of all the batches were found to be of uniform weight variation, ranging from 1.0 ± 0.39 mg to 1.7 ± 0.30 mg. The surface pH of all the implants was found to be neutral and hence no periodontal pocket irritation was expected. The viscosities of the solutions were ranging from 24.34 to 33.45 cps for films F1 to F5. Folding endurance of the films indicate that the formulations have good film properties. Content uniformity studies of the films shows that the drug was uniformly dispersed and recovery was possible to the tune of 90.24 ± 1.46 to 98.42 ± 1.27 % for formulations F1 to F5 and the results are shown in Table 2.

Among the five formulations (F1-F5), F2 possess expected sustained release pattern (i.e., 20.93% at the end of hour 12 hours) the results are shown in Figure 2. Further from the release kinetics it was revealed that the drug release for formulation F2 follows zero order kinetics with release exponent value 'n' 0.543 which shows that the mechanism of release of implant follows Non - fickian diffusion controlled mechanism (peppas) and the results are shown in Table 3.

From the stability studies for best formulation it was revealed that the drug loss was less, though the films were stored for one month. The films were also observed for their appearance and texture. These properties did not change in films during the period of study and the results are shown in Table 4.

Table 1: Formulation of Aceclofenac sodium Implants (mg)

Ingredient	F1	F2	F3	F4	F5
Aceclofenac sodium	100	100	100	100	100
HPMC K 100	50	-	-	-	-
Gelatin	-	50	-	-	25
Ethyl cellulose	-	-	50	-	25
HPMC K 4 M	-	-	-	50	-
Bees wax	10	10	10	10	10
Dibutyl phthalate	2%	2%	2%	2%	2%
Glutaraldehyde	2%	2%	2%	2%	2%
PEG	0.05%	0.05%	0.05%	0.05%	0.05%
Water	q.s	q.s	-	q.s	q.s
Chloroform	-	-	q.s	-	-

Table 2: Physicochemical characterization

Formulation	Length (cm)	Thickness (mm)	Weight variation (mg)	Folding endurance	Moisture loss (%)	Drug content uniformity (%)
F1	0.8 ± 0.00	1.98 ± 0.02	1.1 ± 0.40	32.35 ± 9.147	1.5 ± 0.01	92.45 ± 2.24
F2	0.8 ± 0.00	1.82 ± 0.02	1.2 ± 0.42	54.03 ± 4.253	0.6 ± 0.01	98.42 ± 1.27
F3	0.8 ± 0.00	1.94 ± 0.03	1.1 ± 0.40	48.72 ± 7.220	1.5 ± 0.00	96.24 ± 1.34
F4	0.8 ± 0.00	1.88 ± 0.06	1.0 ± 0.39	38.26 ± 5.263	1.0 ± 0.02	97.84 ± 2.04
F5	0.8 ± 0.00	1.92 ± 0.04	1.7 ± 0.30	26.32 ± 8.480	1.5 ± 0.00	90.24 ± 1.46

* \pm S.D, n=3

Table 3: Kinetic values obtained from different plots of drug-loaded films

Formula Code	Drug release kinetics					
	Zero order		First order		Peppas's	
	K_0	R	K_1	R	n	R
F1	3.4802	0.9452	0.0847	0.7432	0.678	0.9542
F2	4.7234	0.9932	0.0137	0.8255	0.543	0.9946
F3	2.5346	0.9628	0.0732	0.5832	0.586	0.9628
F4	4.2264	0.9482	0.0873	0.7986	0.783	0.9224
F5	2.4032	0.9834	0.0235	0.5984	0.624	0.9432

Table 4: Stability studies for selected formulation (F2)

Physical Parameters	$45 \pm 2^\circ\text{C}/75\% \text{RH}$
Thickness (mm)	1.78 ± 0.02
Length (cm)	0.8 ± 0.00
% Weight variation (mg)	1.0 ± 0.02
Moisture loss (%)	1.6 ± 0.01
Drug content	96.8 %
Drug release	28.19% (at the end of 12 hrs)

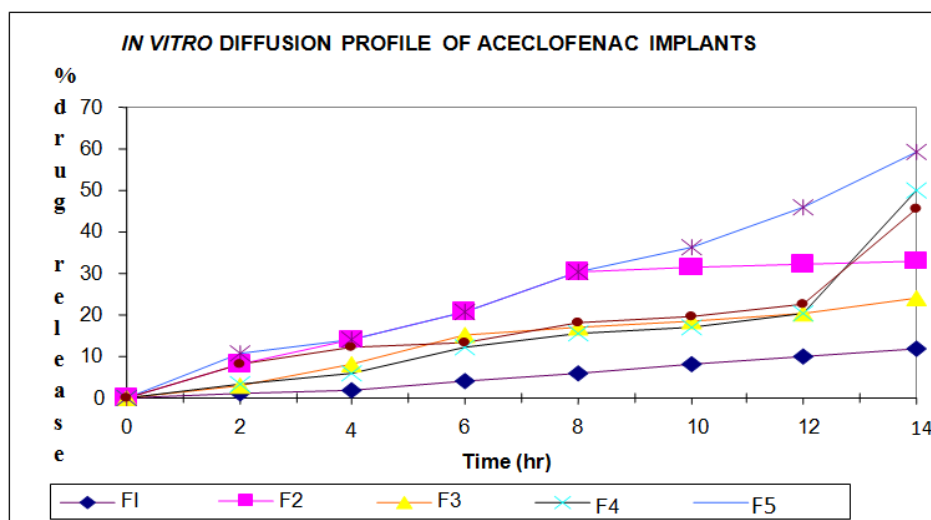


Fig. 1: Cumulative % drug release for Aceclofenac implants F1 - F5

CONCLUSION

The formulation F2 has achieved the objective of formulation of implant drug delivery with prolonged release, decrease dose and frequency of administration, and hence improved patient compliance. From the above study it was concluded that the formulated dental implant can be a best alternate for conventional formulations. The formulated dental implant also cost effective with increased therapeutic efficacy and bioavailability in the aspect of bypassing the hepatic metabolism.

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