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FORMULATION AND EVALUATION OF SATRANIDAZOLE DENTAL STRIPS FOR USE IN PERIODONTITIS

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ABSTRACT

Periodontal strip is a dental device with very small loading dose for site specific one time continuous delivery of drug. Periodontitis is a of inflammatory disease affecting the tissues surrounding the teeth. Periodontitis involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth. This condition is treated using antibacterial agents by oral route. It has been observed that drug administration by this route caused adverse reactions due to high dose. The concept of delivering the drug directly into the periodontal pocket led to the development of local drug delivery systems. This concept gained attention as it requires low dose, produces sustained action and delivers the drug near to or onto the target site. The objective of present study is to formulate and evaluate satranidazole dental strips for use periodontitis. Dental strips were prepared by solvent casting method by using various polymers like, Ethyl cellulose, HPMC K4M, HPC, and Eudragit RL 100 in varying concentrations. The prepared formulations were evaluated for weight variation, thickness, content uniformity, *invitro* drug release studies. Stability studies were formulated with SF7 containing polymers Ethyl cellulose and HPMC K4M was considered as the best formulation based on invitro drug release of 96.43% in 7 days. The formulation found to be stable over a period of three months stability. Further work to done the antibacterial activity of the developed formulation will help to suggest that satranidazole dental strip provide an alternative for use in periodontitis.

KEYWORDS: periodontitis, dental strip, satranidazole, sustain release.

INTRODUCTION

Periodontitis is indicated by signs and symptoms ranging from simple gum inflammation to damage of tissue and bone that support the teeth. Periodontitis can be categorized as chronic periodontitis, aggressive periodontitis and necrotizing periodontitis depending upon the progression of disease. Bacteria and their by-products, directly or indirectly are responsible for triggering host-mediated responses causing injury to gum.[1] Periodontitis progresses from gingivitis or gingival swelling, bleeding and bad breath and later leads to the formation of periodontal pocket thereby causing infection. Periodontal pocket provides ideal conditions for the proliferation of microorganisms: primarily Gram negative and facultative anaerobic.[2] Conventional therapy (scaling and root planning) used for the treatment of periodontitis, but it does not helps to reduce or eliminate bacteria. Chemotherapeutic agents can be administered systemically. Systemic administration of antibiotics require high dose to reach the patient minimum inhibitory concentration. Systemic administration of drugs leads to several adverse effects such as GIT disturbances, hypersensitivity reactions.[3] These draw backs can be markedly reduced if antimicrobial agent to be used locally. The objective of this research was to formulate and evaluates Satranidazole dental strips for placement into the periodontal pockets of periodontitis patients for targeted delivery of drug in order to reduce periodontal pathogens.

In the present work, the goal was to formulate periodontal pocket delivery system containing satranidazole, dispersed in ethyl cellulose (EC), and various copolymers mixtures in different concentrations. Formulated strips were cut into the specified shape and size to make easy insert into the periodontal pocket. EC has been recently demonstrated to sustain the release of drugs. EC has proved itself to use as modified release tablet matrix, as a sustained release film former, and as a thickening agent, and when the nonionic Hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose K4 M (HPMC K4 M), and Eudragit RL-100 copolymers have already been used as excipients of sustained release implant material in dentistry.[4,5]

Satranidazole, a novel nitroimidazole possessing a C-N linkage at C2 of the imidazole ring. The drug produces

extensive DNA damage during reduction, characterized by helix destabilization and strand breakage.[6] Satranidazole falls under class II compounds as per the biopharmaceutical classification system.[7,8] It has low bioavailability and poor aqueous solubility. It is rapidly absorbed and exhibits higher plasma and liver concentration than metranidazole. The MIC90 of Satranidazole against 50 clinical isolates of anaerobes was 0.25 mg/l which was four fold lower than the MIC90 of metranidazole, tinidazole and ornidazole (MIC90 = 1.0mg/l). Hence an attempt was made to formulate and evaluate satranidazole dental strip for use in periodontitis.

MATERIALS AND METHODS

Materials

Satranidazole was obtained as gift sample from Alkem Laboratories Ltd, Mumbai, Ethyl cellulose, HPMC, eudragit; HPC was obtained from SD fine chemicals, India. Dibutylphthalate, chloroform, dichloromethane was purchased from SD fine chemicals, India. Other materials used in the study were of analytical grade.

Preformulation studies

Preformulation study of the drug was carried out to establish its identity and purity which includes λmax of the drug. An absorption maxima of satranidazole was determined using Phosphate buffer, pH 7.4 solution ranging from 5-25µg/ml were scanned from 200-400 nm using UV spectrophotometer.

Preparation method for dental strips

Periodontal dental strips were prepared by solvent casting method. Glass moulds were used for casting the films. ethyl cellulose , eudragit RL-100, hydroxyl propyl cellulose, hydroxyl propyl methyl cellulose were dissolved in chloroform and dichloromethane mixture with a dibutylphalate as a plasticizer in a beaker using magnetic stirrer to get different concentrations polymeric solutions. Into these solutions required quantity of drug was added. After complete mixing, the solution was poured into clean glass mould placed in horizontal plane. The solvent was allowed to evaporate slowly by inverting glass funnel plugged with cotton in the stem at room temperature for 24hrs. After complete evaporation of solvent, cast films were obtained which were then cut into pieces of (0.5×0.5cm), wrapped in an aluminum foil and stored in dark place for further evaluation studies.[9]

Table No. 1 Composition of satranidazole dental strips (SF1 – SF12).

Ingredients (mg)	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9	SF10	SF11	SF12
Satranidazole	227	227	227	227	227	227	227	227	227	227	227	227
Ethyl cellulose	400	400	400	600	600	600	800	800	800	900	900	900
HPMC	25			25			25			25		
HPC		100			100			100			100	
Eudragit RL-100			25			25			25			25
Chloroform**:** Dichloromethane (1:1) QS (ml)	10	10	10	10	10	10	10	10	10	10	10	10
Dibutylphthalate (ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Evaluation of dental strips

Formulated films were subjected to the preliminary evaluation tests. Films with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies. Physicochemical properties such as thickness, weight uniformity, percentage moisture loss, and drug content uniformity of the prepared films were determined.[10,11,12,13]

Weight variation

Individual weights of ten strips of the same size (0.5 x 0.5 cm) were weighed on an electronic balance and the mean weight was calculated. The weight variation of each strip was calculated. The data represented in table No.2

Thickness

Thickness of three strips was measured using micrometer screw gauge. Individual weights of ten strips were noted on an electronic single pan balance .The data represented in table No.2.

Percentage moisture loss

Strips were kept in a dessicator containing anhydrous calcium chloride for three days. After three days, the implants were taken out and re-weighed; the percentage moisture loss was calculated using following equation. The data represented in table No.2.

$$\text{Percentage moisture loss} = \frac{\text{Initial wt-Final wt}}{\text{Initial wt}} \times 100$$

Content uniformity

The strips are dissolved individually in 10ml of dichloromethane in volumetric flasks. The volumetric flask was kept aside till it dissolved. From this 1ml was pipette and diluted. The resulting solution was analyzed spectrophotometrically at 317 nm using phosphate buffer as blank. The data represented in table No.2.

***In vitro* Drug release studies**

- Type of model : static vial method
- Medium : pH 7.4 buffer
- Temperature : 37°c
- Time : 7 days
- Aliquots withdrawn : 3.6 ml for 24 hrs
- Samples were analyzed UV spectrophotometrically at λ max 317nm

Drug release profile of satranidazole was performed by static vial dissolution method. Strips of known weight were placed separately into sealed vials containing 3.6ml of phosphate buffer. The vials were kept at 37±0°C for 24hr. The entire amount of release medium was withdrawn at regular intervals and replaced with freshly prepared buffer.

The concentration of the drug was determined by using UV visible spectrophotometer and this procedure was continued seven consecutive days.

Stability studies

The stability of SF7 was carried out as per ICH guidelines. The formulation was stored 40±2 ^{0}C / 75± 5% RH for 3 months to assess their stability. These containers were stored at different temperatures like for a period of 3 months. All the polymeric films were observed for any physical changes, such as color, appearance, flexibility, or texture, and the drug content was estimated at an interval of 10 days.

***In vitro* drug release kinetics**

Various models were tested for explaining the kinetics the drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, Hixson-Crowell model and Kosmeyer-Peppas release model

RESULTS AND DISCUSSION

To confirm the identity, purity drug for formulation and to establish a drug profile, Preformulation studies were undertaken.

Determination of λ max

The λ max of the drug was found to be 317 nm.

Physicochemical evaluation of dental strips

From the Table 2: the prepared satranidazole periodontal strips were evaluated for their weight variation, thickness, content uniformity, percentage moisture loss. The physico chemical evaluation data indicates that all the strips have uniform thickness and weight. The drug content showed uniform and homogeneous distribution of drug into the strip. Content uniformity of the strips in the range of 81.5±0.02 to 92±0.12.

Table 2. Data of weight variation, thickness. content uniformity and moisture content of SF1 – SF12.

Formulation code	Weight variation (mg)±SD**	Thickness (mm)±SD*	Content uniformity (%)±SD*	% moisture loss±SD*
F1	3.14±0.11	0.12±0.05	80.5±0.05	10±0.5
F2	4.42±0.04	0.13±0.02	85.7±0.02	8±0.15
F3	4.25±0.02	0.15±0.01	89.2±0.06	7.8±1.1
F4	3.36±0.02	0.18±0.02	89.1.±0.03	11±0.5
F5	4.52±0.06	0.12±0.01	91.5±0.02	12±0.69
F6	2.48±0.16	0.28±0.02	87.45±0.01	13±1.6
F7	3.42±0.12	0.17±0.02	92.05±0.12	6±0.06
F8	5.16±0.11	0.15±0.01	89.6±0.08	12±0.69
F9	5.38±0.12	0.18±0.02	90.0±0.06	14±1.47
F10	3.05±0.04	0.13±0.02	89.5±0.08	10±0.5
F11	3.38±0.06	0.16±0.01	88.5±0.06	8±0.15
F12	4.20±0.12	0.15±0.02	90.1±0.05	9±0.03

The cumulative percent drug release data from various formulations of strips were found in the range of 58.38% to 96.43%. Highest percentage of drug release 96.43% was observed from the formulation SF7. The SF7 found to be optimized formulation based on invitro drug release data. The release profile showed that there is slow and sustained release of drug for a period of 7 days Further studies were performed to determine the nature of the drug release pattern from the selected formulation and the drug release data were fitted to various release kinetic models like zero order, first order, Higuchi's model, Korsmeyer-Peppas model. Calculated regression coefficients and is summarized in the table 5. It was found that optimized formulation SF7 follows Higuchi model drug release mechanism.

Table 3. Cumulative % of drug release profile of formulations (SF1-SF6).

Time (hrs)	%Drug Release					
	SF1	SF2	SF3	SF4	SF5	SF6
0	0	0	0	0	0	0
24	25.29±1.10	30.78±0.71	32.45±0.7	20.29±1.14	19.18±0.19	24.29±1.10
48	48.83±0.98	49.36±0.9	50.97±0.8	28.24±1.0	34.63±1.03	46.83±0.98
72	55.39±0.8	66.23±0.9	65.15±0.9	36.18±1.10	46.83±1.10	61.39±0.8
96	65.76±1.43	70.88±0.66	79.36±1.02	43.83±1.0	56.12±1.00	76.36±0.9
120	78.99±0.69	78.29±0.8	82.6±0.8	58.39±0.9	64.95±1.14	85.9±1.01
144	89.41±0.8	86.34±0.6	88.69±0.89	69.12±0.6	76.24±0.73	88.14±0.8
168	90.68±0.89	88.36±0.8	91.64±0.80	78.14±1.04	89.12±0.8	93.15±0.85

Table 4. Cumulative % of drug release profile of formulations (SF7-SF12).

Time (hrs)	%Drug Release					
	SF7	SF8	SF9	SF10	SF11	SF12
0	0	0	0	0	0	0
24	22.36±0.51	30.45±0.7	33.29±1.14	32.18±0.19	31.87±0.86	29.52±0.52
48	34.79±0.46	48.97±0.8	49.24±1.0	54.63±1.03	55.29±0.93	55.34±0.93
72	48.88±0.60	64.15±0.9	69.18±1.10	61.83±1.10	64.42±0.9	68.12±1.02
96	69.12±0.79	72.36±1.02	76.83±1.0	73.12±1.00	77.12±0.96	79.36±0.72
120	86.29±0.68	79.6±0.8	80.39±0.9	80.95±1.14	82.45±1.0	83.62±1.79
144	93.34±0.5	86.64±1.79	87.31±0.68	88.23±0.8	90.24±0.63	91.46±0.50
168	96.43±1.04	90.22±0.87	91.94±0.93	93.10±0.84	92.10±0.68	94.56±0.87

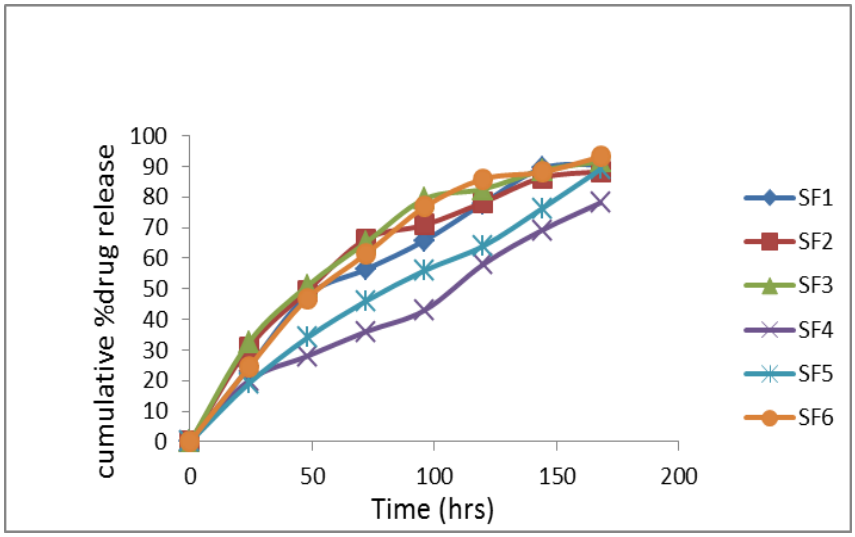

Figure 1. In vitro drug release of periodontal strips SF1- SF6.

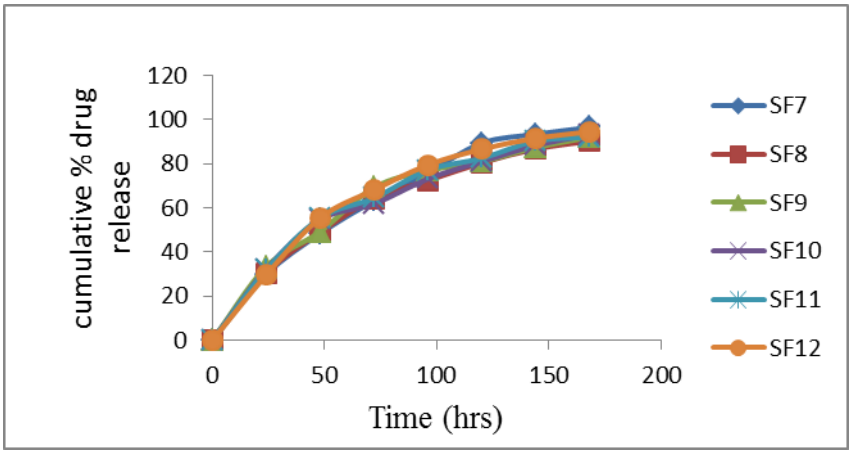

Figure 2. In vitro drug release of dental strips SF7- SF12.

Table 5. Regression coefficient (R^2) of different kinetic models for formulation (SF7).

Model	Regression coefficient (R^2)
Zero model	0.591
First model	0.646
Higuchi model	0.991
Korsmeyer- Peppas	0.634

Stability studies

The amount of drug in the strips was estimated by using UV-spectrophotometer. As per ICH guidelines stability were conducted for the best selected formulation SF7 and it was observed that there was no change in the physical appearance of the best selected formulation.

Table 6. Stability studies data for satranidazole dental strips (SF7).

Time (months)	Physical appearance	Drug content (%) ±SD (n=3)	% Drug release
0	No changes	90.4±0.08	96.32±1.04%
1	No changes	91.3±0.14	96.26±0.04%
2	No changes	93.4±0.17	94.32±0.02%
3	No changes	92.2±0.23	93.25±0.024%

CONCLUSIONS

The formulation SF7 containing ethyl cellulose and HPMCK4M was selected as best formulation based on drug content 92.05±0.12 %and showed *in vitro* drug release of 96.43±1.04 % provide sustain release over a period of 7 days. Further studies are required to demonstrate PK behavior and antibacterial efficacy of the formulation. The prepared dental strips are promising approach to treat periodontists with no side effects and provides sustained action sustain the drug release.

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