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DESIGN, DEVELOPMENT AND CHARACTERIZATION OF LOCAL DRUG DELIVERY SYSTEM FOR TREATMENT OF PERIODONTAL DISEASES.

Vimal Mathew[1]*, Narayanacharylu R[2]

[1] Department of pharmaceutics, National college of Pharmacy, Calicut.

[2] Department of pharmaceutics, NGSMIPS, Mangalore

ABSTRACT: Periodontal disease refers to acute and chronic disorder of soft tissues surrounding the teeth which eventually leads to the loss of the supporting bone. Periodontal diseases progress with age and constitute the major cause of tooth loss in adults. Gatifloxacin is effective against wide range of oral pathogenic organisms. The drug was incorporated into collagen films by means of cross linking with glutaraldehyde. The strips were prepared with two different concentrations of gatifloxacin (i.e., 5% and 10%) with different concentrations of glutaraldehyde i.e., 0.5%, 1%, 2%, and 3% crosslinked for different duration (1,2, 3 and 4 hours) and subjected for various characterization. The strips produced were flexible; possess good tensile strength and hardness. The strips showed an initial burst release and then the release was controlled and extended up to 27 days. Almost all the strips showed release of gatifloxacin above the MIC (1 µg/ml) during the static dissolution study irrespective of percentage of drug.

KEYWORDS: - Periodontal disease, Drug delivery, Gatifloxacin, Dissolution, Glutaraldehyde

1. INTRODUCTION

Periodontal disease refers to acute and chronic disorder of the soft tissues surrounding the teeth which eventually leads to the loss of supporting bone (1). These diseases occur as an inflammatory response due to the overgrowth of anaerobic organisms such as spirochetes and bacteriodes and in some cases micro-aerophillic organisms in the sub gingival plaque. These diseases if unchecked result in the destruction of the bone and soft tissues supporting the tooth (2).

The major periodontal diseases are mucositis, gingivitis, periodontitis and dental caries (3). These diseases can be manifested by clinical signs such as bluish red thickned marginal gingiva, bluish red vertical zone from the gingival margin to the oral mucosa, gingival bleeding and localized pain (4). These are localized infections and can be treated with localized drug therapy.

***Corresponding Author:**
Vimal Mathew
ijin4u@gmail.com

Accumulation of *spirochetes* loaded supra gingival plaque or food particles render the gingival swollen and bleed easily giving rise to gingivitis (5). Periodontitis is a more severe stage of periodontal disease resulting in loss of bone and collagen support of the affected tooth. It is an inflammation of the supporting tissues surrounding tooth caused by pathogenic flora established within the gingival sulcus, which later deepens to become periodontal pocket (6). The pocket provides ideal environment for the growth of anaerobic pathogenic bacteria such as *Actinobacillus actinomycetemcomitans, Bacteroides gingivalis*, *Bacteroides melaninogenicus subspecies intermedius, Eikenella corrodens, Porphyromonas gingivalis, Provetella intermedia* etc (7).

Systemic periodontal antimicrobial therapy is based on the premise that specific microorganism cause destructive periodontal disease and that the antimicrobial agent in the periodontal pocket can exceed the concentration necessary to kill the pathogens (8). Systemic antibiotics can reach microorganisms at the base of deep periodontal pockets and furcation areas via serum and may also af-

fect organisms residing within gingival epithelial and connective tissue (9). With systemic antibiotic therapy there is a considerable variability in the therapeutic activity due to factors like poor absorption in the gastrointestinal tract, first pass metabolism, systemic distribution, bacterial sensitivity and resistance (10).

The increased toxic effects of these elevated dose levels make systemic administration unacceptable due to low benefit to risk ratio. Repeated long term use of systemic antibiotics is fraught with potential danger including resistant strains and super infections (11).

These draw backs can be markedly reduced if antimicrobial agent to be used locally. Because of the smaller dosage used and topical chemotherapy is much safer than systemic chemotherapy in avoiding the side effects of antibacterial agents (12)

The controlled release delivery of antimicrobials directly into periodontal pocket has received greatest interest and appears to hold some promise in periodontal therapy. These delivery systems are produced by immobilizing antibiotic and antimicrobial agents with a carrier substance to provide controlled local release (13)

2. MATERIALS AND METHODS

2.1 Preparation of drug loaded collagen films

Readymade collagen films were cut into 2×2 cm size. The drug gatifloxacin 5% and 10% were added to cross-linking agent glutaraldehyde of different concentrations 0.5%, 1%, 2% and 3%. Collagen films were immersed in the solutions for different time intervals (i.e., 1, 2, 3 and 4hours). These films were then washed with distilled water to remove aldehyde and were allowed to dry at room temperature for 24hours. After drying the films were cut into strips of required size (7 mm in length and 2 mm in width). They were wrapped in aluminium foil and stored in dessicator until further use. Films containing 0% drug (placebo) were also prepared in the similar manner for comparison (14).

2.1.1 Estimation of Drug Content

The strips of gatifloxacin (GATI) of known dimension (7×2mm) were dissolved in 10 ml of acetic acid (1%) and were crushed until the strips dissolved in it. The drug solution suitably diluted with Acetic acid (1%) and the absorbance was measured in UV-Visible spectrophotometer at 290 nm (15).

2.1.2 Weight determination

Twenty strips of the same size (7×2mm) weighed on a single pan balance and the average weight was calculated. This was repeated for six sets of each film and the standard deviation was calculated (14).

2.1.3 Thickness Measurement

The thickness of polymer films was determined by using screw guage. The thickness of each film at different places was determined and the standard deviation was calculated (15).

All measurements (thickness and weight) were determined after residual solvent has been removed from samples by storing the films in dessicator with anhydrous calcium chloride at an appropriate 0% RH and 27 ± 2°C for a week prior to evaluation and testing.

2.1.4 Tensile Strength Measurement

The instrument which was designed in our laboratory was used for the measurement of tensile strength. The strips were clamped at the static end and were attached to the movable rod on railing with the help of a clip. The weights were gradually added to the pan to increase the pull force till the film was cut. The elongation was determined simultaneously by noting the distance travelled by the pointer, before break of the film, on the graph paper. The weight required to break the film was noted as the break force. The tensile strength was calculated using Allen's formula (16).

$$\text{Tensile Strength} = \frac{\text{Break force}}{a \times b} \times \frac{1 + \Delta L}{L}$$

Where a, b, L are width, thickness and length of the test strip respectively and ΔL is the elongation at break

2.1.5 Hardness

The apparatus designed in our laboratory to study the hardness of the strip (Figure 3.4) consists of a wooden stand of 11 cm height and top area of 16×16 cm. A small pan was fixed horizontally on one end of the 2 mm thick iron rod whose other end is reduced to sharp point. A hole of 0.2 cm diameter was made at the centre of the top area of wooden stand for supporting the pan rod. An electric circuit was made through a 3 volt battery in such a way that the bulb lights up only when circuit is completed through the contact of the metal plate and the sharp end of the rod. The film was placed between the metal plate and the sharp end of the rod. The weights were gradually added to the pan at an interval of 10 seconds and for the stabilization of force till the bulb was glown. The final weight was considered as the measure of hardness (17).

2.2 Stability studies

a) The stability of all the strips was studied at different temperatures. The strips of size (7×2 mm) in 3 sets (twelve strips in each set) and the strips were wrapped individually in aluminum foil and also in butter paper and placed in petridishes. These dishes were stored at ambient humidity condition at room temperature (27 ± 2°C), oven temperature (45° ± 2°C) and in refrigerator (5 - 8°C) for a period of 10 weeks. The samples were analysed for physical changes like colour texture. The drug content was estimated by UV/Visible spectrophotometer at 290 nm.

b) The stability of drugs was also confirmed by scanning samples in UV/Visible spectrophotometer.

2.3 In vitro release studies

2.3.1 Static Dissolution Studies

Sets of 6 strips of known weight (GATI) were placed separately into small test tubes containing 1 ml of phosphate buffer pH 6.6. The tubes were sealed and kept at 37° C for 24 hours. The buffer was then drained off and replaced with a fresh 1 ml phosphate buffer pH 6.6. By employing a double bean UV/Visible spectrophotometer, concentration of gatifloxacin in the buffer removed from and around each strips was measured at 290 nm. The procedure was continued until the drug is completely removed (19).

3. RESULTS AND DISCUSSION

The strips produced were flexible and easily removable. The amount of drug added to the aldehyde solution did not change the polymer characteristics. It was also observed that there were no signs of crystallization when the drug concentration was raised from 5% to 10%.

Gatifloxacin loaded collagen strips showed thickness ranging from 0.043 to 0.059 mm in case of 5% drug concentration and 0.059 to 0.069 mm in case of 10% drug concentration respectively. There is no much significant difference among the strips in thickness due to use of commercially available collagen and collagen being a proteinous material, exhibited a closer packing arrangement

When drugs were incorporated, the tensile strength of polymer films was decreased. The tensile strength for plain strips was 2085.56 gm/sq.mm. The tensile strength of cross linked collagen strips are found to be varying from 965.146 gm/sq. mm to 1675.568 gm/sq. mm in case of 5% drug and 940.225 to 1478.567 gm/sq.mm in case of 10% drug concentration respectively.

It was also found that the tensile strength is reduced with increase in concentration of glutaraldehyde and increase in duration of cross-linking.

The amount of drug present in the strips was determined using the methods described in previous chapter materials and methods. The drug loading was found to be ranging from 41.259 µg to 94.856 µg in case of 5% drug concentration and 104.32 µg to 164.66 µg in case of 10% drug concentration respectively. From the above data it is evident as the concentration of drug and duration of

cross-linking were increased; the percentage of drug loading was also increased. There is a variation in drug loading in the strips. The difference in drug content may be due to change in percentage of drug incorporated and duration of cross-linking.

3.1 *In vitro* release studies

All most all non eroding controlled release dosage forms provided commercially and described in the literature use drug dissolution, diffusion and transport across the membrane or the matrix, thus as long as there is a sufficient drug solubility these mechanism control the drug release (20-23)

4. CONCLUSION

Periodontal diseases progress with increase in age and constitute major cause of tooth loss in adults. Periodontits is the most severe stage of disease resulting in the resorption of alveolar bone and detachment of periodontal ligament supporting the tooth. System antibiotic therapy may cause various side effects. Hence, a controlled release local drug delivery system targeting the site of action with be beneficial in the long term treatment commercially available collagen strips were impregnated with drug solution and then cross linking was attempted. Cross linking is necessary to reduce the burst effect and to extend the drug release for more number of days, so that the same formulation be used for prolonged period. As the concentration of cross linking agent and time of cross linking was increased, the tensile strength of drug loaded ships were reduced, where as hardness was increased. The cross linked collagen strips showed release of drug up to 25 days for 5% drug and 27 days for 10% drug. The drug release was found to be zero order. The release pattern followed Higuchi's equation, indicating the diffusion controlled release. Throughout the release studies the strips remain intact without any disintegration. The average release (i.e., from 4th day to 27days is 3.25 µg/ml) which is above minimum inhibitory concentration of gatifloxacin

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