

# FORMULATION AND CHARACTERIZATION OF CURCUMIN PERIODONTAL FILMS FOR LOCAL DELIVERY OF ANTIMICROBIALS

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## Abstract

A novel periodontal film for the treatment of periodontitis was developed in the present work, for local delivery of herbal drug Curcumin was used, which is effective against infecting microorganisms in the periodontal pocket. Calibration curves for Curcumin was developed in phosphate buffer PH 6.6, FT-IR investigations demonstrated that the chosen drug and polymers had no interaction. Thermal analysis technique accomplished for identification of various physical properties and thermal transitions of drug and the polymeric materials. Periodontal films were prepared by solvent casting technique using Eutragit and HPMC as polymers, Dibutyl phthalate as plasticizers and PEG 800 as surface active agent. The formulated periodontal films were assed for folding endurance, percent moisture loss, surface pH, viscosity, thickness, uniformity of weight, content uniformity as well as in-vitro release. To explain release kinetics, evidence of in-vitro delivery from constructed periodontal films was fitted into various equations and kinetic models. Zero first-order equations and Higuchi models were employed as kinetic models. By fitting the data to the Korsmeyer-Peppas model, the release mechanism was discovered. The optimal formulation (F 4) was placed in vivo to study in vivo drug release by placing Curcumin periodontal film(F 4) in rabbit's gingival sulcus for 14 days and the drug release was analysed by HPLC method. The AUC peaks showed that the drug concentration was sufficient enough to inhibit the growth of bacteria.

**Keywords:** Curcumin periodontal film, Periodontitis, Controlled release and Gingivitis.

## INTRODUCTION

Periodontal diseases are well recognised as a serious global public health concern. It is impossible to stress the importance of everyday dental care in preserving healthy teeth and gums. Periodontal disease can affect anyone of any age, ethnicity, colour, gender, or socioeconomic status. Gingivitis and periodontitis are hazardous periodontal diseases that, if left untreated, can result in tooth loss. Periodontal is a term that literally means "around the tooth." Periodontal disease is an infection of the gums and bone that supports the teeth caused by bacteria. Periodontitis can affect a single tooth or a group of teeth. It starts when bacteria in plaque (the sticky, colourless film that grows on teeth all the time) inflames the gums. Periodontal disorders can range from minor gum inflammation to severe disease. 1 Periodontitis is a condition in which the alveolar bone around the teeth gradually deteriorates, leading to tooth loosening and eventual tooth loss if left untreated. Germs that attach to and proliferate on the surfaces of the teeth, as well as an overly aggressive immune response to these microorganisms, cause periodontitis.2 Periodontitis is diagnosed by probing the soft gum tissues around the teeth with a probe and visually inspecting x-ray films to assess the degree of bone loss. Periodontists are periodontitis specialists, and their profession is known as "periodontology" or "periodontics." Periodontal disease is caused by bacterial plaque, a sticky, colourless coating that forms on teeth over time. Smoking, cigarette use, inheritance, pregnancy and puberty, stress, medicines, clenching or grinding teeth, diabetes, and a poor diet are all factors that contribute to periodontal disease. Periodontal pathogens can only thrive in environments where the atmosphere and nutritional content are ideal for their growth, and once established, the disease causes significant changes in

the periodontal microenvironment. In healthy gingival sulci, the flow of gingival crevicular fluid (GCF) is extremely modest, but it quickly increases to 3.5 ml/day or more. *Bacteroides gingivitis*, *Bacteroides melanogenic* sub species *intermedius*, *Porphyromonas gingivitis*, and *Prevotella intermedia* are the most typically cultured anaerobic pathogenic bacteria. The presence of bluish red thickening marginal gingiva, a bluish red vertical zone from the gingival boundary to the oral mucosa, gingival bleeding, and localised pain might all be signs of periodontal pockets.. 3,4,5.

FIGURE 1: Representing the healthy gums, gingivitis, periodontal disease and periodontitis.



## MATERIALS AND METHOD:

### Materials

Curcumin was obtained as the gift sample from Prakriti products pvt ltd Ankola, HPMC, Eudragit RL100, Dibutyl phthalate alcohol was obtained from laboratory.

### Preparation of standard stock solution of Curcumin in phosphate buffer PH 6.6

The curcumin standard stock solution was made by dissolving precisely weighed 100mg of drug in a small amount of phosphate buffer PH 6.6 in a 100ml volumetric flask volume was made up to 100ml by using phosphate buffer PH 6.6 to obtain the solution 1000 $\mu$ g/ml, and 1ml of the standard stock solution was pipetted into a 10ml volumetric flask and made up to the mark with phosphate buffer PH 6.6 The maximum wavelength of curcumin was discovered to be 410 nm.<sup>8</sup>

### Preformulation studies:

#### Drug polymer compatibility

Pure drug and polymer FTIR investigations were conducted. To generate mixes, 3 mg of pure medication and 3 mg of polymer HPMC Eudragit triturated were mixed with 97 mg of KBR in a smooth mortar, then placed in the instrument's sample container and scanned in IR spectroscopy between 400 and 4000  $\text{cm}^{-1}$ . The acquired spectrum was examined for any drug-polymer interactions. There was no interaction demonstrated.<sup>6</sup>

## Differential Scanning Calorimetric Studies

Differential scanning calorimetric analysis was used to determine the compatibility and physical condition of pharmaceuticals inside the optimised formulation (F4) (DSC). A differential scanning calorimeter was used to create the thermograms (Mettler, Toledo, 822e). The instrument was calibrated using 5 mg of indium heated at 10°C per minute<sup>1</sup>. The thermal behaviour of 2–10 mg of samples was investigated by heating them in a hermetically sealed pan with a pinhole in the lid at a rate of 10°C min<sup>1</sup> from 25°C to 300°C under a nitrogen purge of 20 ml min<sup>1</sup>.<sup>7</sup>

Method of preparation of Curcumin periodontal films:

1. Curcumin was dissolved in polyethylene glycol and polymer HPMC and eurtagit was dissolved in alcohol at room temperature using magnetic stirrer in separate beaker and beaker containing drug solution was mixed with polymers solution.
2. Later dibutyl phalate was added as plasticizer.
3. The solution was poured on a petri dish and dried at room temperature.
4. The films were cut into appropriate sizes, covered in aluminium foil, and stored in desiccators after being removed from the petri dish..<sup>8</sup>

Formulation containing Curcumin periodontal films

Table 1: composition of Curcumin periodontal films.

| Ingredients           | F1  | F2  | F3  | F4  |
|-----------------------|-----|-----|-----|-----|
| Curcumin(mg)          | 100 | 100 | 100 | 100 |
| HPMC(mg)              | 100 | 100 | 125 | 150 |
| Eudrgit RL100 (mg)    | -   | 75  | 100 | 125 |
| Dibutyl phthalate(ml) | 1   | 1   | 1   | 1   |
| PEG 800 (ml)          | 5   | 5   | 5   | 5   |
| Alcohol(ml)           | 10  | 10  | 10  | 10  |

## EVALUATION OF THE FILMS:

Periodontal films are characterised physically.

Thickness and weight variations. The thickness of the films was measured with a screw gauge. Three films were chosen at random and their thicknesses were measured with a screw gauge. Individual values can differ by up to 5% from the average. Selected films from each formulation having a surface area of 1 cm<sup>2</sup> were used. To determine weight variation, 10 patches of each formulation were weighed separately on an electronic balance, and the average weight of the patch was calculated. <sup>9</sup>

PH of the surface

Periodontal patches were allowed to swell for 1 hour on the surface of agar plates, which were made by dissolving 2% (w/v) agar in distilled water while stirring, then placing the solution into a Petri dish to gel and harden at room temperature. The recorded readings or the mean of five measurements were utilised to determine the surface PH using PH paper put on the swollen region. The films' PH was tested using PH paper on an agar plate, and it was found to be around PH 7. The surface PH of all of the films was determined to be neutral, indicating that there would be no periodontal pocket.<sup>10</sup>

Folding endurance

It was determined by folding the patch in the same area until it broke or was folded 300 times, which was deemed enough to

relieve good film properties. The patch was folded 300 times in the same location without breaking, demonstrating excellent folding endurance. The test was repeated five times on all films. 10

#### Percentage moisture loss

Individually weighed films were maintained in a desiccator containing calcium chloride at room temperature. The films were weighed several times until they indicated a consistent percentage moisture loss, then the % moisture loss was determined using the formula below.10

$$\text{Percentage moisture loss} = \frac{(\text{initial weight} - \text{final weight})}{\text{initial weight}} \times 100$$

#### Viscosity

The viscosity of these solutions was evaluated using a Brookfield viscometer (L VDE-E model) attached to the Heli path spindle number 18 and a solution containing the identical quantities of medication, polymers, and plasticizer as the produced films. The viscosity was measured at 100rpm at room temperature. The figures recorded were the average of five different measurements.6

#### Drug content uniformity of films

Patches (1x1 cm<sup>2</sup>) were cut from various regions of the films and placed in a 10ml volumetric flask with 10 ml ethyl alcohol, which was then set aside until the patch was completely dissolved. With PH 6.6 phosphate buffer, 1 ml of the solution was diluted appropriately. The solution's absorbance was measured at 410 nm, with a blank polymer solution. 6

#### Scanning Electron Microscopic Studies

The surface morphology of the drug-loaded film was studied using scanning electron microscopy. The film sample was placed on metal stubs using a double-sided adhesive band to produce proper electrical conductivity, and then gold was sputtered on the specimen. The images were taken using environmental mode and an ET detector with a 10 kV excitation. 11

#### Study of drug release in vitro

Since the PH of gingival fluid is between 6.5 and 6.8, and the films remain immobile in the periodontal pocket, a phosphate buffer with a pH of 6.6 was used as the simulated gingival fluid. A static dissolving method was employed for in-vitro drug release investigations by taking the patch of size (1X1 cm<sup>2</sup>) were placed in tiny test tubes containing 1ml phosphate buffer (pH 6.6). The tubes were sealed and stored at 37° C for 24 hours. The buffer was emptied and refilled with 1 mL of PH 6.6 phosphate buffer. The drug concentration in buffer was then measured at 410nm. For 9 days, in-vitro drug release tests were conducted.8,14

#### Kinetic research

The in vitro diffusion experiments data was fitted into zero order and first order to analyse the drug release kinetics and mechanism from the films.

Kinetics of zero order: The following equation can be used to depict drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the substance slowly, providing that the area of the dose does not change and no equilibrium condition is established.

$$Q_t = Q_0 + K_0t$$

Where  $Q_t$  represents the amount of drug dissolved in time  $t$ ,  $Q_0$  represents the starting amount of drug in the solution, and  $K_0$  represents the zero order release constant.

Kinetics of first order : The drug data were fitted into the following equation to analyse first order rate kinetics.

$$\log Q_t = \log Q_0 + K_1 t / 2.303$$

Where  $Q_t$  represents the amount of drug released during time  $t$ ,  $Q_0$  represents the initial amount of drug in the formulation, and  $K_1$  represents the first order release constant.

Higuchi model: Higuchi created many theoretical models to investigate the release of water soluble and partially soluble medicines contained in semisolids and solid matrices. The equation  $Q_t = K_H \cdot t^{1/2}$  was used to derive mathematical formulas for drug particles dispersed in a uniform matrix behaving as diffusion media.

$K_H$  is the Higuchi diffusion constant, and  $Q_t$  is the amount of medication released in time  $t$ .

#### In vivo Animal studies:

An in vivo animal investigation was conducted to investigate drug release. The ethical committee gave their approval. 8–12 weeks/ 1.5 kg male Albino rabbit (New Zealand rabbit) Each rabbit was sedated with 2% xylazine-HCl (5 mg/kg body weight) and ketamine-HCl (Ketasol, 30 mg/kg body weight, administered intramuscularly). The surgery room was cleansed and disinfected. A 1cm<sup>2</sup> periodontal patch was applied to the gingival sulculus of each rabbit's bottom incisors. The gingival crevicular fluid of the lower cleaned incisors was extracted with a #30 standardised sterile paper point on days 1, 2, 4, 7, 10, and 14, the gingival crevicular fluid of the lower incisors was removed using a #30 standardised sterile paper point. During each treatment, the paper point was placed 1 mm into the gingival crevice and remained in place for 30 seconds. The paper point was eluted with 0.1 ml phosphate buffer solution immediately after collection and kept at -20°C until analysis.

#### HPLC Analysis:

An HPLC column with a C18 detection wavelength of 410 nm and UV detection at 410 nm was used to analyse curcumin. The mobile phase was acetonitrile and water (50:50 v/v) acidified with 2 percent acetic acid at a flow rate of 1.2 mL min<sup>-1</sup>. The curve range was linear for the concentration range of 0.5–75 g mL<sup>-1</sup>.

#### Standard and working solutions

Curcumin was dissolved in methanol to a final concentration of 1.0 mg μL<sup>-1</sup> in a 20.0 mL volumetric flask. In an ultrasonic bath, the solution was sonicated for 5 minutes before being finished to the final volume. Working solutions (0.5–75.0 μL<sup>-1</sup>) were made by diluting aliquots of the standard solution in a 5.0 mL volumetric flask with methanol (1.0 mg mL<sup>-1</sup>).

## RESULTS

Curcumin was dissolved in phosphate buffer PH 6.6 and scanned between 200 and 450 nm. With  $y = 0.16665x + 0.0192$  and  $R^2 = 0.9795$ , the  $\lambda_{max}$  was discovered to be in the 410nm range. Displayed in (figure 2)

Table 2. Curcumin calibration curves at 410 nm in phosphate buffer (pH 6.6)

| Concentration(μg/ml) | Absorbance (410nm) |
|----------------------|--------------------|
| 0                    | 0                  |
| 1                    | 0.166±0.123        |
| 2                    | 0.325±0.224        |
| 3                    | 0.570±0.136        |
| 4                    | 0.768±0.456        |
| 5                    | 0.857±0.834        |
| 6                    | 0.946±0.103        |

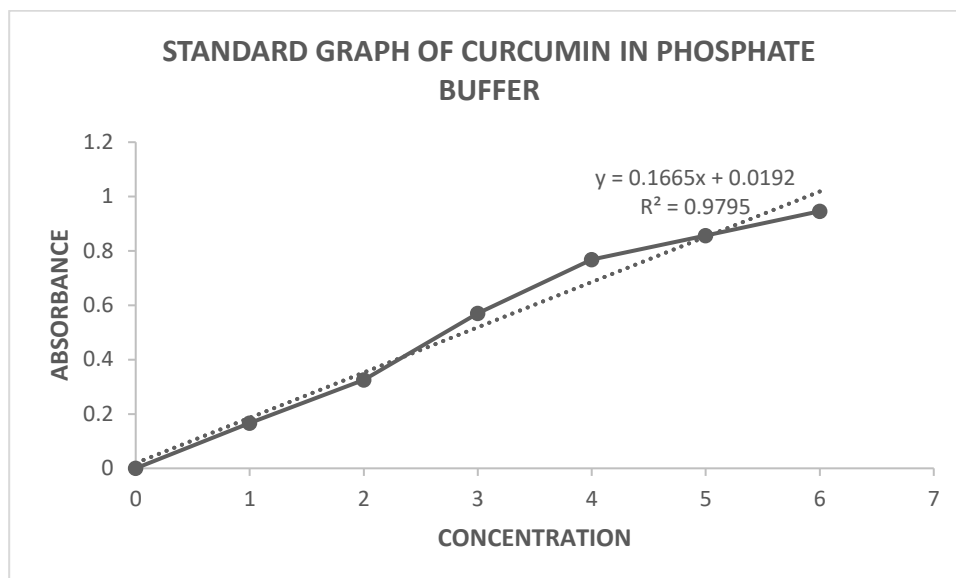


Figure 2. Standard graph of Curcumin in phosphate buffer P H 6.6

### FTIR Spectroscopy

Pure drug and drug polymer mixture FTIR investigations were conducted, and the pure drug exhibited C=C 1600 cm<sup>-1</sup> stretching C-O stretching at 1222.68 cm<sup>-1</sup>, OH group stretching at 3407.64 cm<sup>-1</sup>, C=O stretching at 1537 cm<sup>-1</sup>, CH bending at 999.58 cm<sup>-1</sup>. The identical peaks were seen in the same region of the spectrum, indicating that the drug and polymer had no interaction (figure 3).

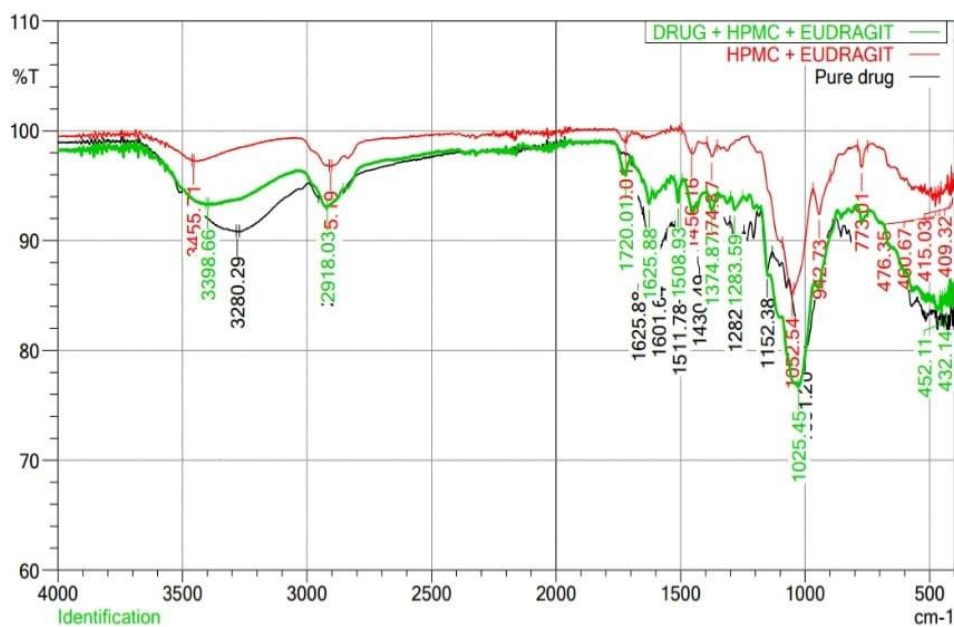


Figure 3. FTIR of Curcumin and polymer combination

### DSC Study

DSC studies showed sharp endothermic peak of pure Curcumin at 174.17° C which is attributed to melting point of Curcumin

crystals (figure 4). With the admixture of polymer sharp endothermic peak was observed at 174.17 °C showing the melting point of Curcumin crystals and at broad peak at 363.34 °C due to the water evaporation by polymer used (figure 5). Hence DSC study suggested that Curcumin was in crystalline form in optimized formulation F4

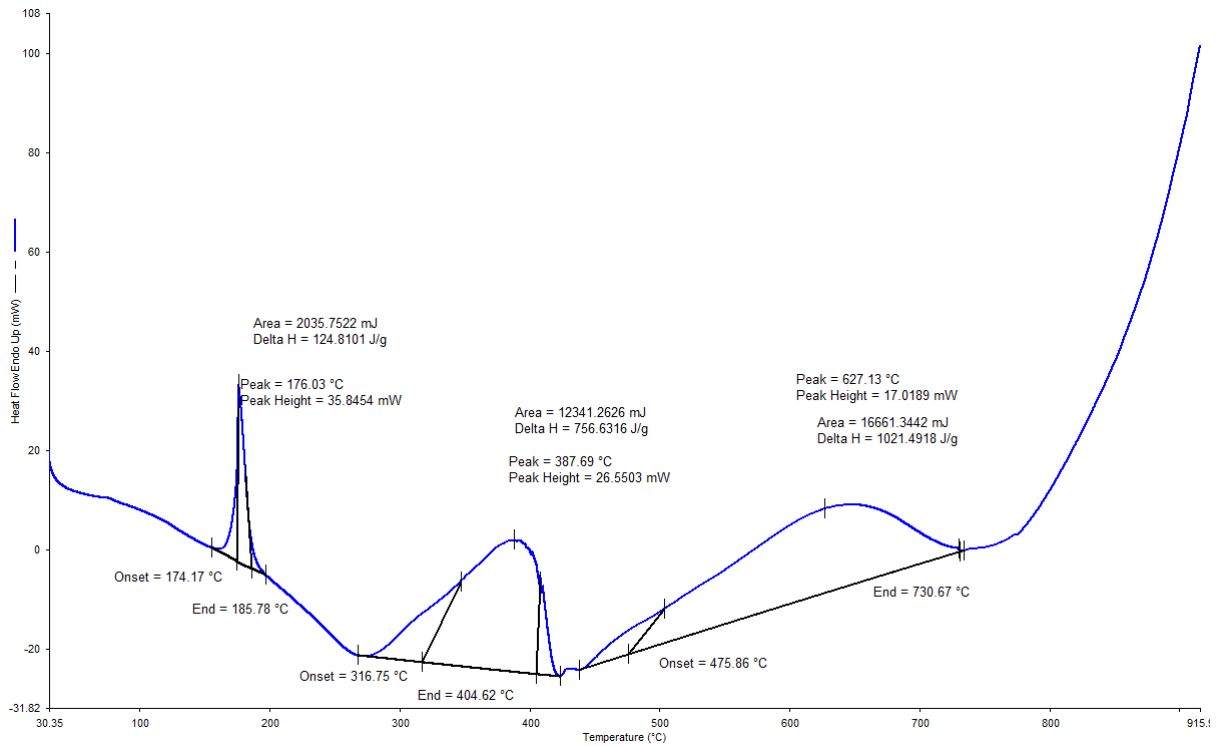


Figure 4. DSC of Pure Curcumin

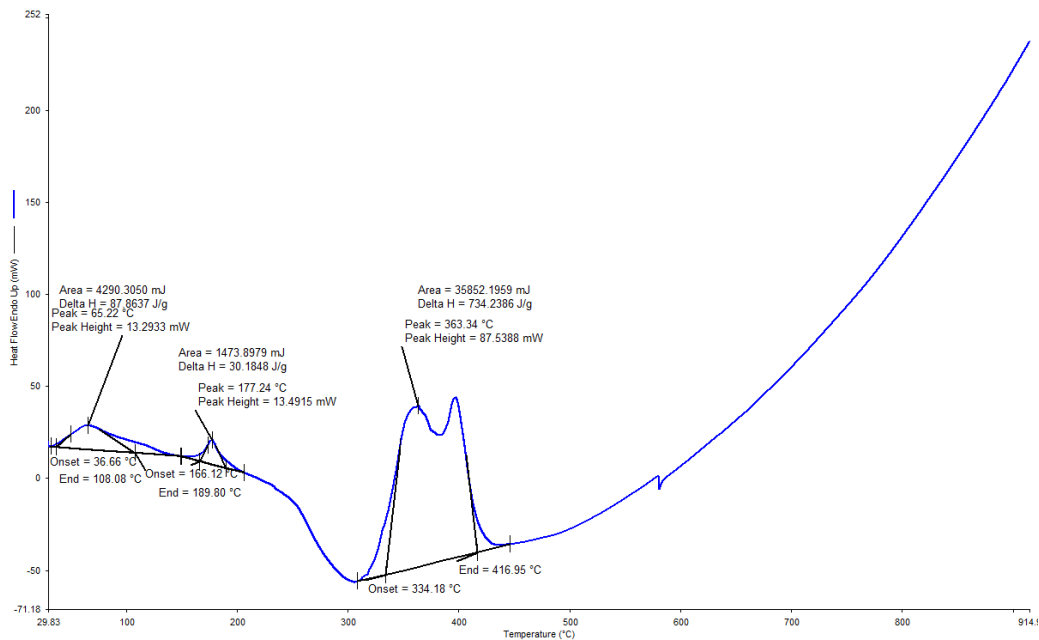


Figure 5. DSC of Pure Curcumin HPMC and Eutragit

### Physical characterization of periodontal films

Thickness uniformity of films was carried the average thickness was in the range of 0.14±0.12 to 0.2±0.23 mm. Uniformity of

weight of films were carried the values were found to be varying from range of  $0.763\pm 0.11$  to  $0.786\pm 0.25$  mg PH paper on an agar plate was used to evaluate the PH of all the films surfaces, which was found to be around 7. All of the films' surface PH was determined to be neutral, indicating that no periodontal pocket irritation was expected. The films' folding durability was greater than 250 times. This indicates that all of the formulas have a high folding endurance. On all of the prepared films, percentage moisture loss was measured, and it ranged from 7.103 to 10.91. F4 revealed a maximum moisture loss of 10.91, which could be attributable to the polymers' higher water vapour permeability. The films' viscosities were measured to be between  $10.12\pm 0.156$ -  $13.66\pm 0.427$ . F4 had the greatest rate of 13.66 cps, which could indicate that this is related to the polymers' higher water vapour permeability. The drug content uniformity was tested at 410 nm, and all of the formulations showed a drug loading of more than 90%, indicating that much of the medication was not lost and was uniformly spread (table 3)

Table number 3: Physical characterization of periodontal films

| Formulation | Thickness      | Weight variation | Surface pH | Folding endurance | Percentage moisture loss | Viscosity        | Drug content uniformity |
|-------------|----------------|------------------|------------|-------------------|--------------------------|------------------|-------------------------|
| F 1         | $0.14\pm 0.12$ | $0.763\pm 0.11$  | Neutral    | $280\pm 1.15$     | 7.103                    | $10.12\pm 0.156$ | 95.748                  |
| F 2         | $0.16\pm 0.24$ | $0.770\pm 0.21$  | Neutral    | $285\pm 1.08$     | 8.244                    | $11.8\pm 0.328$  | 99.091                  |
| F 3         | $0.18\pm 0.25$ | $0.778\pm 0.24$  | Neutral    | $285\pm 1.62$     | 9.53                     | $12.76\pm 0.232$ | 93.012                  |
| F 4         | $0.2\pm 0.23$  | $0.786\pm 0.25$  | Neutral    | $285\pm 1.77$     | 10.91                    | $13.66\pm 0.427$ | 98.179                  |

### Sem study

Surface electron microscopy revealed that the drug appeared on the carrier matrix's surface as white specks in optimised films. (Figure 7). On the placebo film, there were no comparable particles. (Figure 6) The surface characteristics of the film from which the drug was released were examined, and pore formation in the polymer matrix was discovered, indicating drug release. (Figure 8) The films had a smooth surface prior to drug release, but surface imperfections were visible afterward, according to SEM. There were also some irregular pores. The formation of pores in the drug-loaded film formulation revealed that Curcumin release began with drug dissolution and then followed diffusion through the pores.

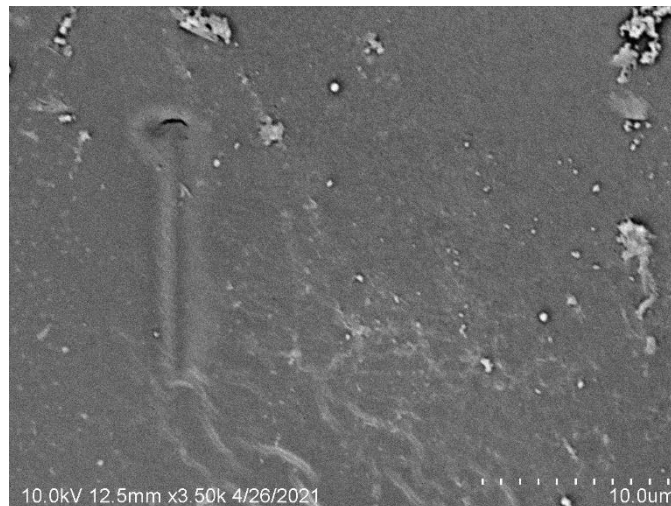


Figure 6. SEM of Placebo

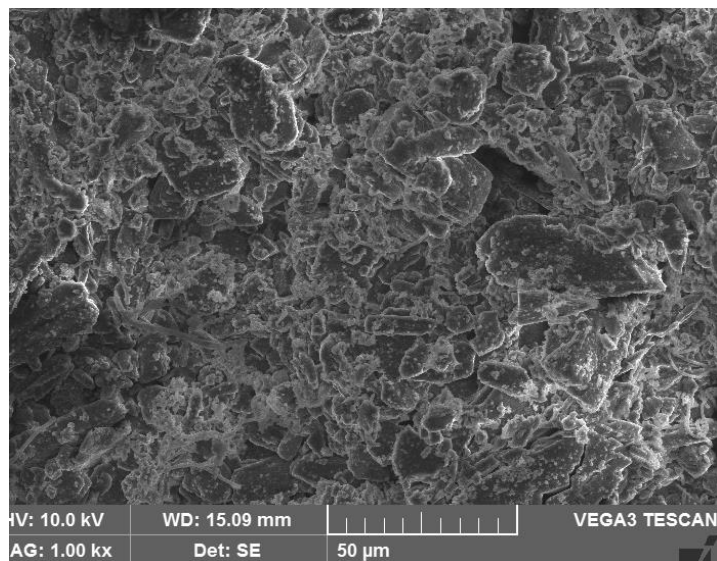


Figure 7. SEM of Curcumin drug loaded film F4

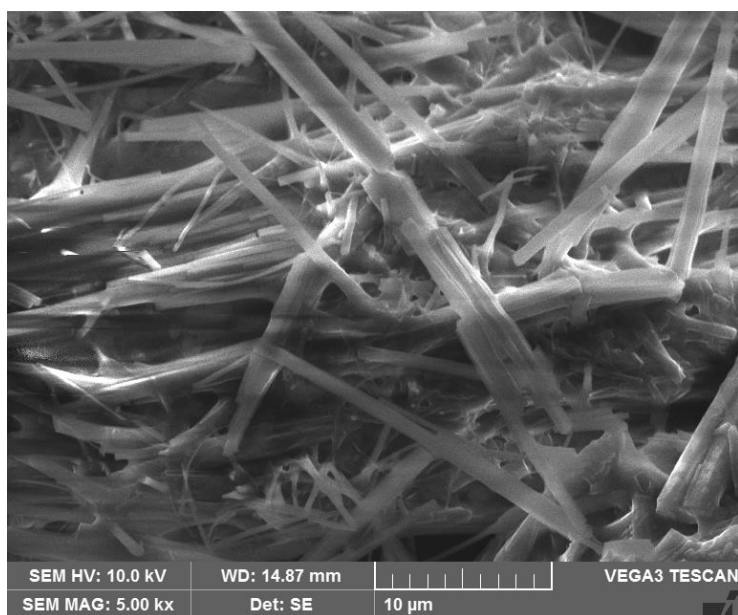


Figure 8. SEM of Curcumin drug loaded film F4 after dissolution

#### In vitro drug release

It was tested for 9 days in a phosphate buffer with a pH of 6.6 and found to be between 88.50 to 99.88 percent. The maximum release was 99.88 percent in F4..

Table number 4: Comparative In-vitro drug release study of Curcumin patch from F1-F4

| Time(days) | % of drug released of F 1 | % of drug released of F 2 | % of drug released of F 3 | % of drug released of F 4 |
|------------|---------------------------|---------------------------|---------------------------|---------------------------|
| 0          | 0                         | 0                         | 0                         | 0                         |
| 1          | 0.76                      | 36.24                     | 36.38                     | 42.24                     |
| 2          | 49.94                     | 48.42                     | 54.20                     | 59.23                     |
| 3          | 62.27                     | 66.25                     | 60.41                     | 75.58                     |
| 4          | 68.13                     | 72.43                     | 75.64                     | 81.47                     |

|   |       |       |       |       |
|---|-------|-------|-------|-------|
| 5 | 72.98 | 84.29 | 81.27 | 89.78 |
| 6 | 80.25 | 88.02 | 87.92 | 93.44 |
| 7 | 83.78 | 92.12 | 91.23 | 96.93 |
| 8 | 86.76 | 94.64 | 93.50 | 99.88 |
| 9 | 88.50 | 95.90 | 96.39 | ----- |

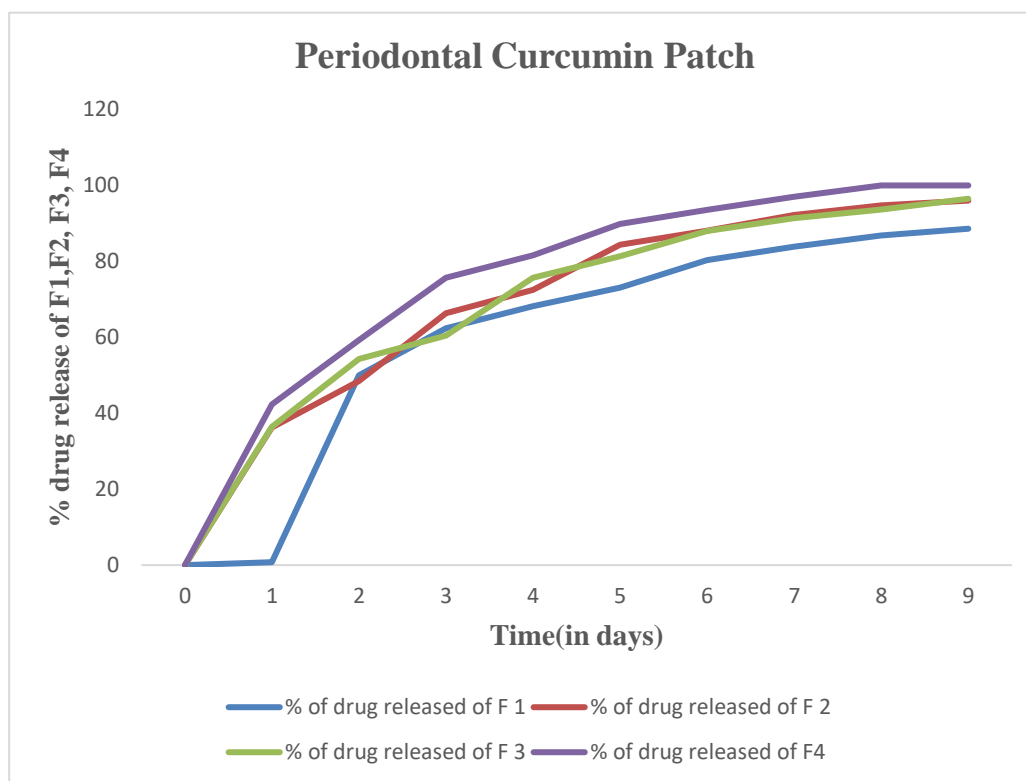


Figure 9: Comparative In-vitro drug release study of Curcumin patch.

#### Kinetic study

The kinetic study data predict drug release followed first order as the R<sup>2</sup> values were higher in first order. The data was fitted into Higuchi's as the model to confirm the exact process of drug release from the periodontal film the R<sup>2</sup> values were in the range of 0.8069 -0.8489 which showed the release followed diffusion rate-controlled mechanisms (table 5).

Table number 5 : Showing the Zero order, First order and Higuchi model of Curcumin patch from F1-F4

| Film code | Zero order   | First order                                     | Higuchi model                               |
|-----------|--|---|---|
| F1        | y = -<br>9.8866x+85.439<br>R <sup>2</sup> = 0.8069 | y=-<br>0.1083x+1.9809<br>R <sup>2</sup> =0.9676 | y =9.8866x+4.6747<br>R <sup>2</sup> =0.8069 |
| F2        | y = -<br>9.4861x+75.067<br>R <sup>2</sup> =0.8489  | y=-<br>0.1528x+1.9959<br>R <sup>2</sup> =0.9956 | y =9.4861x+15.447<br>R <sup>2</sup> =0.8489 |
| F3        | y = -<br>9.3223x+74,511<br>R <sup>2</sup> =0.8474  | y=-<br>0.1498x+1.9948<br>R <sup>2</sup> =0.9932 | y=8.4347x+19.717<br>R <sup>2</sup> =0.8346  |
| F4        | y = -<br>9.2939x+68.912<br>R <sup>2</sup> =0.7861  | y=-<br>0.2752x+2.1817<br>R <sup>2</sup> =0.8668 | y=10.613x+16.81<br>R <sup>2</sup> =0.828    |

## In vivo Animal Study

The optimized formulation of Curcumin (F4) was placed in rabbit's gingival sulcus and studied for the drug release above formulation was carried out for 14 days (Figure 10)



Figures no 10. Insertion of the patch in gingival sulculus of rabbit's lower incisors

## HPLC Analysis

The HPLC approach was utilized to evaluate drug release *in vivo*, and it was found to be suitable for the analytical assessment of Curcumin concentrations in rabbit gingival crevicular fluid. Standard Curcumin had a retention duration of 15.723 minutes (Figure 11), while Curcumin (F4) had a retention time of 16.128 minutes (Figure 12). The calibration curve was shown to be linear over the concentration range of Curcumin (0.5 to 75  $\mu\text{g mL}^{-1}$ ) and This method was successful in identifying low levels of Curcumin in rabbit gingival crevicular fluid..AUC values varying from 754 to 95332 (table.5) The concentrations were sufficient enough to inhibit the growth of bacteria in periodontal cavity.

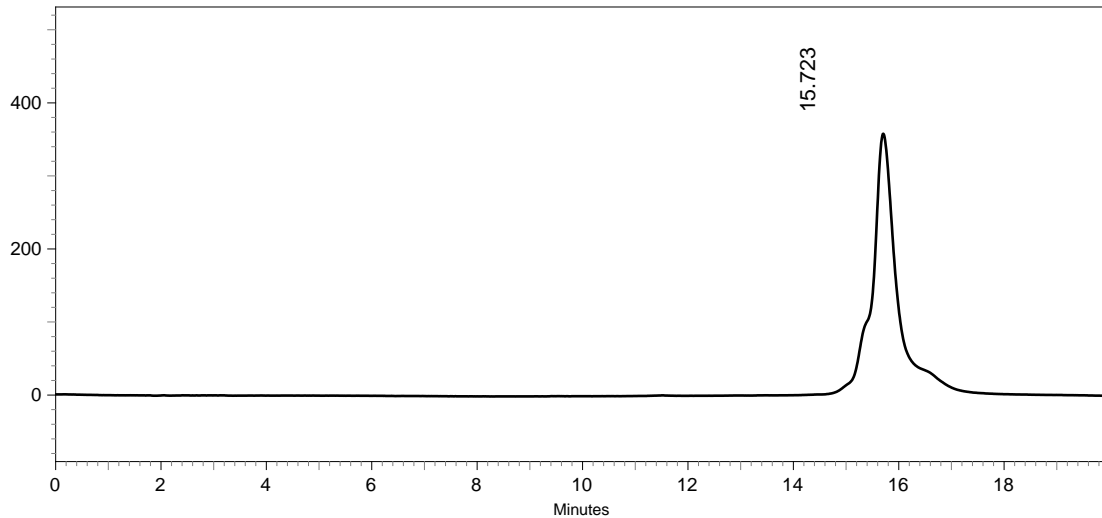


Figure no 11: HPLC Standard peak of Curcumin

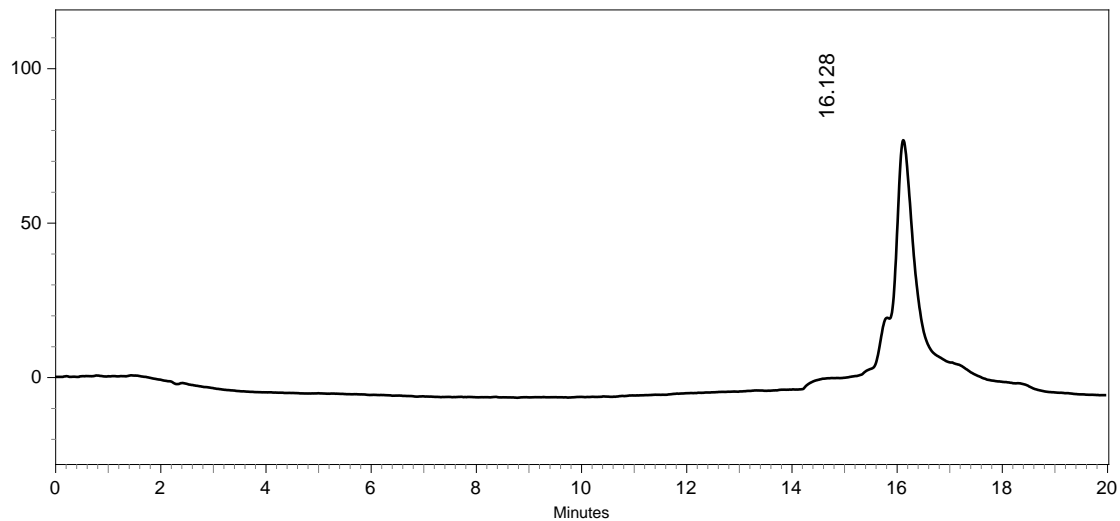


Figure no 12: HPLC peak of Curcumin containing periodontal films

Table number 5 : Showing Time in days and AUC.

| Time in days | AUC Curcumin periodontal film |
|--------------|-------------------------------|
| 1            | 754                           |
| 2            | 764                           |
| 4            | 9468                          |
| 7            | 12662                         |
| 10           | 328206                        |
| 14           | 95332                         |

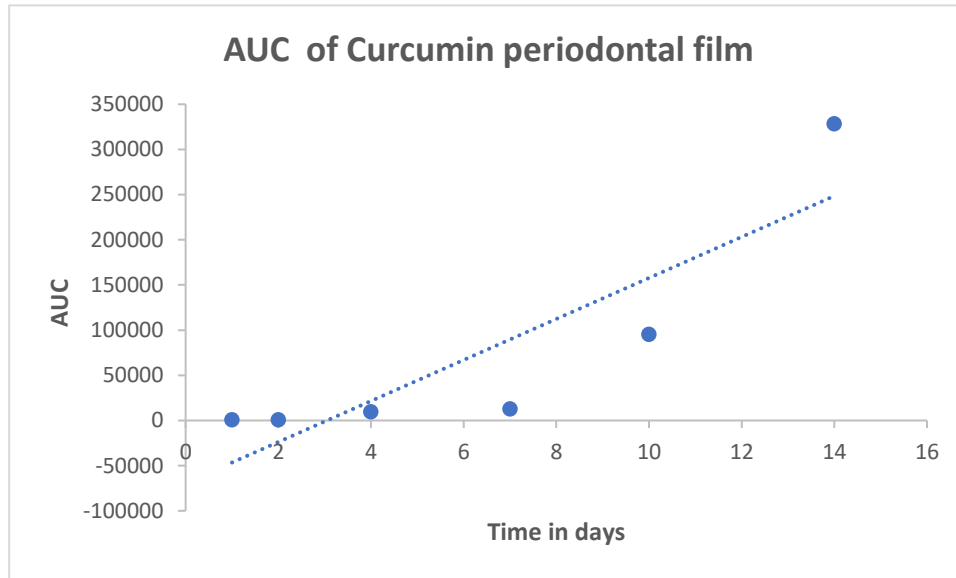


Figure no 13: AUC and Time in days of Curcumin containing periodontal films

## DISCUSSION

Curcumin has a  $\lambda_{max}$  of 410nm in phosphate buffer PH 6.6, with  $y=0.16665x+0.0192$  and  $R^2 = 0.9795$ . The findings of FTIR investigations on pure drug and polymer demonstrated that there was no interaction between the two. DSC studies were done to know the thermal behaviour of pure Curcumin and the drug with polymer mixture revealed a sharp endothermic peak of pure Curcumin at 174.17°C, which is attributable to Curcumin's melting point, and a similar peak in the mixture at the same location. Hence the thermal behavior did not affect the formulation. Thickness uniformity, uniformity of weight, The surface PH, The folding endurance, percentage moisture loss, viscosities all the parameters were in acceptable limits. The drug content uniformity was above 90% in all formulation. Surface Electron Microscopy was performed on placebo, drug loaded film and drug film after dissolution. Prior to drug release, the films exhibited a clean surface, but surface defects were obvious later, according to SEM. There were also some pores that were not straight. The formation of pores in the formulation of a drug-loaded film suggested that Curcumin release began with drug dissolution and then followed diffusion through the pores. In vitro drug release was studied for 9 days and the range of 88.50-99.88% F4 showed the maximum release of 99.88%. Kinetic study revealed that all formulations followed First order reaction as  $R^2$  values were greater than zero order release and mechanism of release followed diffusion rate-controlled mechanisms. In vivo Animal studies were performed using Albino rabbit for 14 days. The optimized formulation of Curcumin periodontal patch (F4) was placed in rabbits gingival sulcus and gingival fluid was extracted and analyzed by HPLC method. AUC showed the concentration was able to inhibit the microorganism in the periodontal cavity.

## CONCLUSION

Periodontal patch containing herbal drug was successfully formulated using HPMC and Eutrgit as the rate controlling polymers. All the parameters were in acceptable limits. In vivo animal studies performed also showed that the drug release was effective

against microorganisms in the periodontal cavity. Hence F4 is considered as the best formulation.

## CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation.

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