FORMULATION, DEVELOPMENT AND EVALUATION OF CEFEXIME TRIHYDRATE PERIODANTALFILMS FOR MANAGEMENT OF PERIODONTITIS

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ABSTRACT
Local therapy has three potential advantages: decreased drug doses, increased drug concentration at the site of infection, and reduced systemic side effects such as gastrointestinal distress. Treatment of periodontitis with a localized drug delivery system aims at delivering therapeutic agents at a sufficient level inside the periodontal pocket and at the same time minimizes the side effects associated with systemic drug administration. Hence, drug delivery systems containing antibacterial agents are used for delivery to the periodontal pocket. For the present study, cefixime trihydrate(CFT) is selected as a model drug. CFT is third-generation cephalosporin antibacterial agent which acts on third & last cell wall synthesis To prepare and evaluate dental film containing cefixime trihydrate for the treatment of periodontitis to achieve more concentration of drug at the site, thereby reducing drug toxicity and drug resistance developed by organisms. The drug was incorporated into Chitosan and fabricated as a film in three altered concentrations 10, 20, and 30% w/w to the weight of the polymer. The films containing the drug content (10, 20, & 30% w/w) were further cross-linked with glutaraldehyde 2%, which was aimed to extend and control the drug release for more number of days. The in-vitro release studies showed an initial burst release of the drug by more than 40% and the release was sustained up to seven days and 12 days for the non-cross-linked and cross- linked films, respectively. Through the % release study, the films persisted intact, without any disintegration.

Keywords: cefixime trihydrate**,** Periodantalfilms Periodontal diseases

I. INTRODUCTION

I.I. Periodontal diseases

The term ‘periodontal diseases’ covers an extensive diversity of chronic inflammatory conditions of the gingiva (or gums, the soft tissue adjacent to the teeth), bone, and ligament (the connective tissue collagen fibers that anchor a tooth to the alveolar bone) backup the teeth. A periodontal disease initiates with gingivitis, the local inflammation of the gingiva that is commenced by bacteria in the dental plaque, which is a microbial biofilm that forms on the teeth and gingiva. In this Briefing, the term gingivitis denotes to plaque-convinced gingivitis. Chronic periodontitis occurs when untreated gingivitis develops to the loss of the gingiva, bone, and ligament, which generates the deep periodontal ‘pockets’ that are a symbol of the disease and can ultimately lead to tooth loss. Periodontal disease may add to the body’s overall inflammatory burden, waning conditions such as diabetes mellitus and atherosclerosis**. [1]**

I.II. Types of periodontal diseases [2]

1. Inflammation: A localized defensive response provoked by injury or demolition of tissue, which serves to terminate, dilute, or wall off both the injurious agent and the injured tissue. A cellular and vascular reaction of tissues to injury

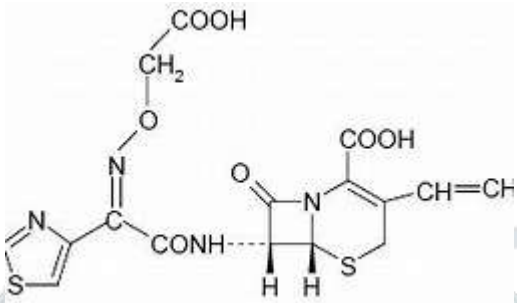
2. Gingivitis: The gingival Inflammation

3. Periodontitis: Inflammation of the supportive tissues of the teeth. Typically increasing destructive modification projecting to loss of bone and periodontal ligament. A delay of inflammation from gingiva into the adjacent bone and

ligament

4. Adult Periodontitis: A type of periodontitis that generally has a start elsewhere age 35. Bone resorption typically progresses gradually and principally in the horizontal direction. Well-known local environmental issues are prominent and abnormalities in host resistance have not been found.

5. Juvenile Periodontitis: Might be generalized or localized; onset during the circumpubertal period; familial distribution; the relative paucity of microbial plaque; less acute signs of inflammation than would be probably based upon the harshness



Mechanisms of resistance: Bacterial resistance to cefixime may be due to one or more of the following mechanisms: Hydrolysis by extended-spectrum beta-lactamases and / or by chromosomally-encoded (AmpC) enzymes that may be induced or de-repressed in certain aerobic gram- negative bacterial species. The reduced affinity of penicillin-binding proteins. The reduced permeability of the outer membrane of certain gram-negative organisms restricting access to penicillin-binding proteins.[4]

Drug efflux pumps more than one of these mechanisms of resistance may co-exist in a single bacterial cell. Depending on the mechanism(s) present, bacteria may express cross-resistance to several or all other beta-lactams and / or antibacterial drugs of other classes.

II. MATERIALS:

Cefixime trihydrate are gifted by Adora product Pvt. Ltd. Aurangabad and all other ingredients from Research lab fine chem. Industries Chitosan, Ethylcellulose, Polyvinyl pyrrolidine K30, PEG:400, Dibutyl phthalate, Chloroform, Methylene chloride, Ethanol (95%), Potassium dihydrogen phosphate, Sodium hydroxide, Agar powder, Beef extract, Peptone, Acetone.

III. METHOD:[5]

1.1. Preparation of CFT loaded chitosan film

Chitosan (2 g) was soaked in 100 ml aqueous acetic acid solution (1% v/v) for 24 hours to get a clear solution, which was later filtered through a muslin cloth to remove undissolved polymer (chitin). Ciprofloxacin (0, 10, 20, and 30 % w/w based on the weight of chitosan) was incorporated in 100 ml of chitosan solution and vortexed for 15min. The viscous dispersion was kept aside for 30 min for complete expulsion of air bubbles. Films were cast by pouring the drug-polymer solution into the Petri plate wrapped with aluminum foil and allowed to dry at room temperature. The dry films were cut into strips of (7×2 mm),

wrapped in aluminum foil, and stored in a calcium chloride desiccator at room temperature for pending evaluation.

Figure 1: CFT Periodontal film F2

Figure 2: Image of 7x2 mm size film strips

1.2 Preparation of cross-linked chitosan films

The films containing 30% CFT were cross-linked by exposure to glutaraldehyde vapor in a chromatography chamber. The chamber was previously saturated with the vapor of 2%v/v glutaraldehyde for 24h; the films were exposed to the vapor for 2 and 4 h, respectively, and then dried. The dry films were cut into strips (7 × 2 mm), wrapped in aluminum foil, and stored in a calcium chloride desiccator for further study.[6]

Figure 3: Film solution exposed to Glutaraldehyde vapor

Table No.1: Composition of CFT periodontal film with cross-linking time in 2% Glutaraldehyde

Sr. No	**Ingredient**	**Batch code**									
		F1 CT	F2 CT	F3 CT	F4 CT	F5 CT 4hr CL	F6 CT 2hr CL	F7 CT 4hr CL	F8 CT 2hr CL	F9 CT 4hr CL	F10 CT 2hr CL
1	CFT (% w/w of polymer wt)	0.0	10	20	30	30	30	20	20	10	10
2	Chitosan (gm)	2	2	2	2	2	2	2	2	2	2
3	GAA(ml)	1	1	1	1	1	1	1	1	1	1
4	Purified water (ml)	Qs up to 100 ml	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

IV. EXPERIMENTAL WORK[7,8]

1. Preformulation Studies of CFT

Color: white to light yellow.

Nature: crystalline in nature.

2. **Solubility determination**: Solubility determination by using different solvents methanol, ethanol (95%), ethyl acetate & in cold water. The solubility parameter is reported in **table no.4**

3. **Loss on drying**:

The LOD of CFT was determined by taking 1.00 gm & dried in an oven at 100-105°c for 4hr. LOD is calculated using the following formula:

LOD = (Initial wt.-Final wt) / (Initial wt.)*100.

4. **Preparation of Solutions:**

pH 6.8 Phosphate buffer:

Place 50.0 ml of 0.2 M potassium dihydrogen phosphate in a 200 ml volumetric flask, add the 22.4 ml 0.2M NaOH & then add H2O to final volume.

0.2 M Potassium dihydrogen Phosphate: 27.218gms of potassium dihydrogen phosphate, as added in 1000ml volumetric flask containing distilled water and volume, was added up to mark with distilled water.

0.2 M Sodium Hydroxide: 8 gms of NaOH were added in 1000ml volumetric flask containing distilled water and volume was added up to mark with distilled water.

5. **Determination of λ max of CFT in pH 6.8 phosphate buffer.**

Stock Solution: Dissolve 100 mg of CFT in 6.8 phosphate buffer in 100 ml volumetric flask & pipette out 10 ml of the previous solution, makeup volume up to 100 ml with 6.8 phosphate buffer.

Scanning: Drug concentration 12µg/mL solution was made up using the above stock solution in pH 6.8 phosphate buffer and scanned in UV at 200 nm-400nm wavelengths and spectrum was taken. It was found that the absorption maxima of CFT was 289.0 nm and used for further studies.[9]

6. A standard plot of CFT in pH 6.8 phosphate buffer

Procedure: From stock solution (100mg/ml) aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1.0ml, 1.2ml, were transferred to volumetric flask of 10mL and finally dilution was made up with phosphate buffer- 6.8 pH and scanned in UV at 287nm.concentration ranges and data are reported in **Table no.5** calibration graph was plotted using this data and same is reported in **Fig no.15.**

7. Determination of λ max of CFT in distilled water.

Stock Solution: Chlorhexidine gluconate in aqueous solution (100 gm/ml)

Scanning: From the stock solution,10µg/ml of drug solution was prepared using distilled water and scanned at a 200nm-400nm wavelength in UV. Spectrum absorption maxima of CFT was observed at 289.0 nm it was used for further studies.[10]

8. A standard plot of CFT in distilled water

Procedure: From stock solution (100µg/ml) aliquots of ,0.2 mL,0.4mL, 0.6mL, 0.8mL, 1.0mL, and 1.2mL were transferred to serious of 10ml volumetric flask and volumes were made up using dist. H_2O. the absorbance of these solutions was measured at 287nm.concentration ranges and data are reported in Table no.7.calibration graph was plotted using this data and the same is reported in **Fig no.16**.[23]

9. Determination of Partition coefficient:

It is a measure of lipophilicity of atom, which can be utilized as an expectation of how well it will have the capacity to cross the biological membrane. Standout amongst the most widely recognized methods for measuring part coefficient is the shake cup strategy.[11]

Procedure: Place 10 mg CFT in 5 ml water-saturated with 5 ml n-octanol to aqueous and oily phase, drug solution had been shaken about 6hr.This was allowed to keep stable at R.T for 12 hr. This mixture was separated into two different layers using separating funnel. Then each layer was scanned in UV for CFT concentration. Partition coefficient K may be written as,

K = (Concentration of solute in organic phase) / (Concentration of solute in water phase)

Figure 4: Shake Flask Method using Separating Funnel

10. Drug- excipients Compatibility Study by FTIR:

In dosage forms like gels and films, there are chances of drug excipients interaction because of the interaction of drug and polymer which may even lead to instability of drug. Preformulation studies in regards to medication excipients similarity are in this way extremely discriminating in selecting suitable excipients. It was conceded using FTIR[12] spectrophotometry. FTIR spectra of CFT, chitosan & CFT with chitosan is reported in **fig no. 17, 18,& 19** respectively.

11. Drug- excipients Compatibility Study by DSC

DSC was employed to study ant potential change in CFT that the drug may have experienced during its processing into periodontal films. Thermal analysis was performed by DSC of the formulation using a differential scanning calorimeter. The DSC thermograms of CFT, chitosan & CFT with chitosan [13]

V. Evaluation of periodontal films [15,16,17]

Formulated films were subjected to the preliminary evaluation tests. Films with any imperfections entrapped air or difference in thickness or weight were excluded from further studies.

1. **Morphological properties films:** All films were visually inspected for properties such as smoothness size, & color.

2. **Weight uniformity of dental films:** Film (size of 7×2 mm^2) was taken from different areas of film and the weight variation of each film was determined. Data is reported in **table no.14**

3. **Thickness uniformity of dental films**: The thickness of each film was measured using vernier caliper at different positions of the film & average was calculated. Data is reported in table no.14

4. **Swelling index (SW) of dental films:** Periodontal films were individually weighed (W1) and placed in an agar plate, stirred, and the solution was poured into the Petri dish till it solidifies at room temperature and examined for an increase in weight. After 15 minutes intervals for 1 hour, films were removed from the gel plates and excess surface water was removed carefully using tissue paper. The swollen films were then reweighed (W2), and the swelling index (SW) was calculated using the following formula. Data is reported in table no15.

SW = ((W 2 – W 1) / W 1) × 100

Where,

W 1 = the weight of film at time zero W 2 =

the weight of swollen film[30]

.

Figure 5: Image of Swell films in 2% agar media after 1hr

5. **Percentage moisture loss (PML) of dental films:**

Percentage moisture loss was determined by keeping the films (7×2 mm in a desiccator containing anhydrous calcium chloride. After 3 days, the films were taken out, reweighed and the percentage moisture loss was calculated using the following formula. Data is reported in table no.14

Percentage moisture loss (PML) = (Initial weight –Final weight) / Initial weight) × 100

6. Drug content uniformity of films:[18]

Content uniformity was determined by taking previously weight film in a volumetric flask & warm buffer solution 37°c was added in small portions the flask was kept in the shaker for 4 hr & then the final volume was adjusted to 100 ml with the buffer. The flask was undisturbed for one hr & 5 ml of the supernatant portion was taken in a 25 ml volumetric flask diluted to 5 times in buffer. The turbid solution was centrifuged & absorbance was read at 289.0 nm. on a
U.V spectrophotometer. Observed drug content is reported in **table no.14.**

***7.In vitro* drug release of dental films:**

Since the pH of gingival fluid lies between 6.5 – 6.8, phosphate buffer pH 6.8 was used as the simulated gingival fluid. Also since the film should be immobile in the periodontal pocket, a static dissolution model was adopted for the dissolution studies. Sets of 10 films of known weight and dimension were placed separately in small sealed test tubes containing 5.0 ml of phosphate buffer (pH 6.8) and kept at 37 ± 0.5°C for 24 h. The buffer was then drained off and replaced with a fresh 2.5 ml of buffer. The concentration of drug(s) was determined by UV/VIS spectrophotometer at 289.0nm the procedure was continued for 7 and 12 consecutive days for non crosslinked and crosslinked films, respectively.% drug release of uncrosslinked & crosslinked value are reported in table no.16 & 17 resp.% drug release plotted using this data & the same [19]

***8.In vitro* drug release kinetic studies:**

To analyze the in vitro release data various kinetic models were to describe the release kinetics. The zero-order rate Equation no: (1) describes the systems where the drug release rate is independent of its concentration. The first order Equation no: (2) describe the release from the system where the release rate is concentration-dependent. Higuchi described the release of drugs from the insoluble matrix as a square root of the time-dependent process.[20]

1. Zero-order model[21]

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_t = Q_0 + K_0 t \qquad (1)$$

Where

Q_t is the amount of drug dissolved in time t,

Q_0 is the initial amount of drug in the solution (most times, ($Q_0 = 0$), and K_0 is the zero-order release

constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as

The cumulative amount of drug released versus time

Application: This relationship can be used to describe the drug dissolution of several types of

Modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc.

2. First-order model[22]

This model has also been used to describe the absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first-order kinetics can be expressed by the equation:

where K is the first order rate constant expressed in units of time^{-1}.

$$\log C = \log C_0 - Kt / 2.303 \qquad (2)$$

where C_0 is the initial concentration of a drug, k is the first-order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303.

Application: This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

3. Higuchi model[23,24,25]

The data obtained were plotted as cumulative percentage drug release versus square root of time.

Application: This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water-soluble drugs.

VI. RESULT & DISCUSSION 1.

Solubility determination of CFT

Table no.2: Solubility determination of CFT using various solvents

Sr.no.	Solvent	Solubility
1	Coldwater	Insoluble
2	Methanol	Completely soluble
3	Ethanol	Completely soluble

2. Loss on drying of CFT

LOD = (Initial wt.-Final wt) / (Initial wt.)*100.

(42.43-42.33) / (42.43)*100

LOD = 0.23%

3. Determination of λ max of CFT in phosphate buffer- pH 6.8.

Scanning of drug solution was carried out in the UV range (400-200nm) by using a UV- visible spectrophotometer. In phosphate buffer- pH 6.8, a sharp peak was at 289nm Sharp peak was observed at 289.0 nm using pH 6.8 phosphate buffer as a solvent and concluded that the drug has λ max 289.0 nm. The absorbance of concentration ranges of 0.2-12 (µg/ml) has been analyzed at 289 nm

A standard plot of CFT in 6.8 pH phosphate buffer

Table no.3: Conc. Vs absorbance of CFT in 6.8 pH phosphate buffer

Sr.no.	Conc^{n}. µgm/ml	Absorbance(nm)
1	2	0.128
2	4	0.237
3	6	0.337
4	8	0.434
5	10	0.528
6	12	0.642

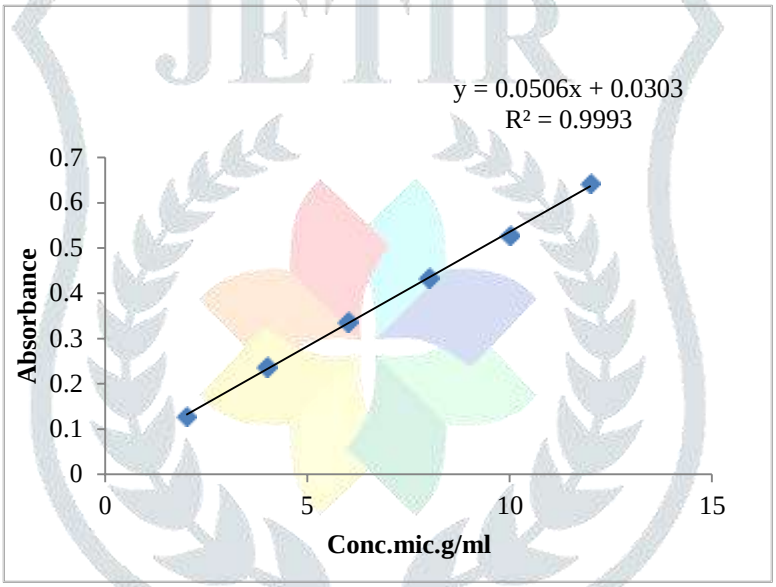


Figure 6: A standard plot of CFT in pH 6.8 phosphate buffer.

Table no.4: Summery Report of calibration curve for CFT in 6.8 phosphate buffer

Sr. No	Parameter	Cefixime trihydrate
1	Wavelength (λ max)	289.0 nm
2	Beer's limit (µg/ml)	0.2-12
3	Corrélation coefficient (R^2)	0.0999
4	Slope	0.0506
R^2 value shows linear		

Discussion:-

The calibration curve was obtained by using the 0.2-12 µg/mL solution of CFT in 6.8 phosphate

buffer. The absorbance was measured at 287 nm. The calibration curve for **CFT was** shown in figure no.17. The absorbance obtained for the given concentrations was shown in Table no.9. The calibration curve 15 shows regression equation Y= 0.0506x +0.303 and R^2 value 09993.The result revealed that drug concentration between 0.2 – 12 µg/ mL follows Beer Lambert's law as the regression coefficient was 0.999.

4. Determination of λ max of CFT in distilled water.

Scanning of drug solution was carried out in UV range (400-200nm) by using a UV-visible spectrophotometer. The sharp peak was observed at 289 nm using distilled water as a solvent and concluded that the drug has λ max 289nm. The absorbance of concentration ranges of 0.2-12(µg/mL) was measured at 289 nm and reported in **table no.11**

Table no.5: The standard plot of CFT in distilled water

Sr.no	Conc. µgm/ml	Absorbance
1	2	0.102
2	4	0.221
3	6	0.319
4	8	0.427
5	10	0.518
6	12	0.612

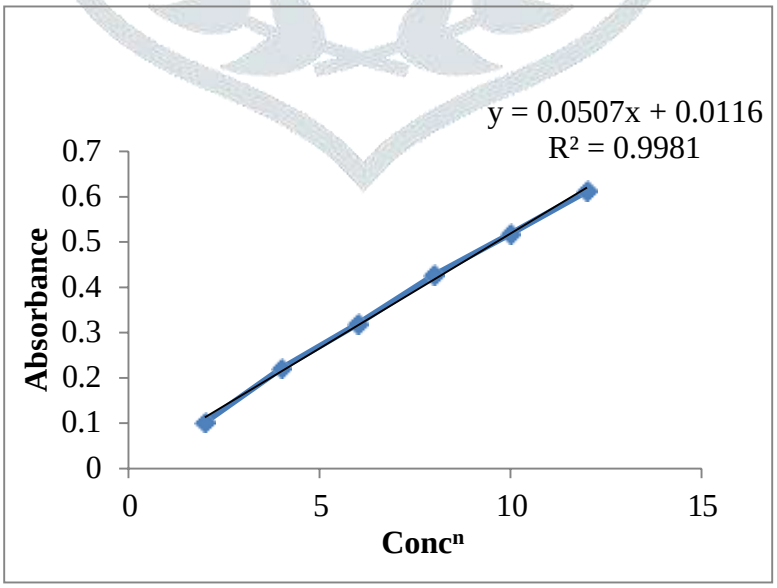


Figure 7: The standard plot of CFT in distilled water.

Table no.6: Summary Report of a calibration curve for CLT in distilled water

Sr. No	Parameter	CFT
1	Wavelength (λ max)	289nm
2	Beer's limit (µg/ml)	0.2-12
3	Corrélation coefficient (R^2)	0.9981
4	Slope	0.0507
r^2 value shows linear		

5. Determination of partition coefficient:

The partition coefficient between water and n-octanol is the most broadly utilized measure of substance compound lipophilicity. Shake cup system was utilized for partition coefficient determination and afterward, two stages were isolated, and amassing of medication (CFT) in the watery stage and oil stage was resolved by UV Spectroscopic method. Partition coefficient P may be written as,

K = (Concentration of solute in organic phase) / (Concentration of solute in water phase) The partition coefficient of CFT was found to be **0.1069** in *n*-butanol distilled water.

CFT- excipients Compatibility:

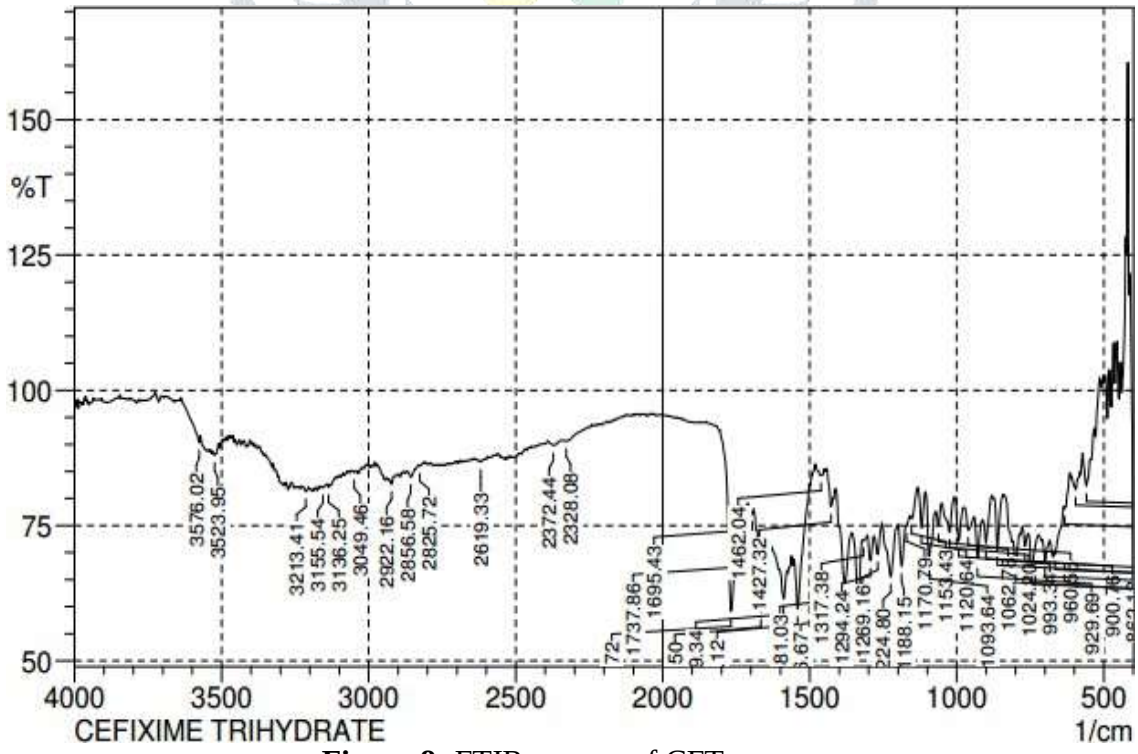


Figure 8: FTIR spectra of CFT

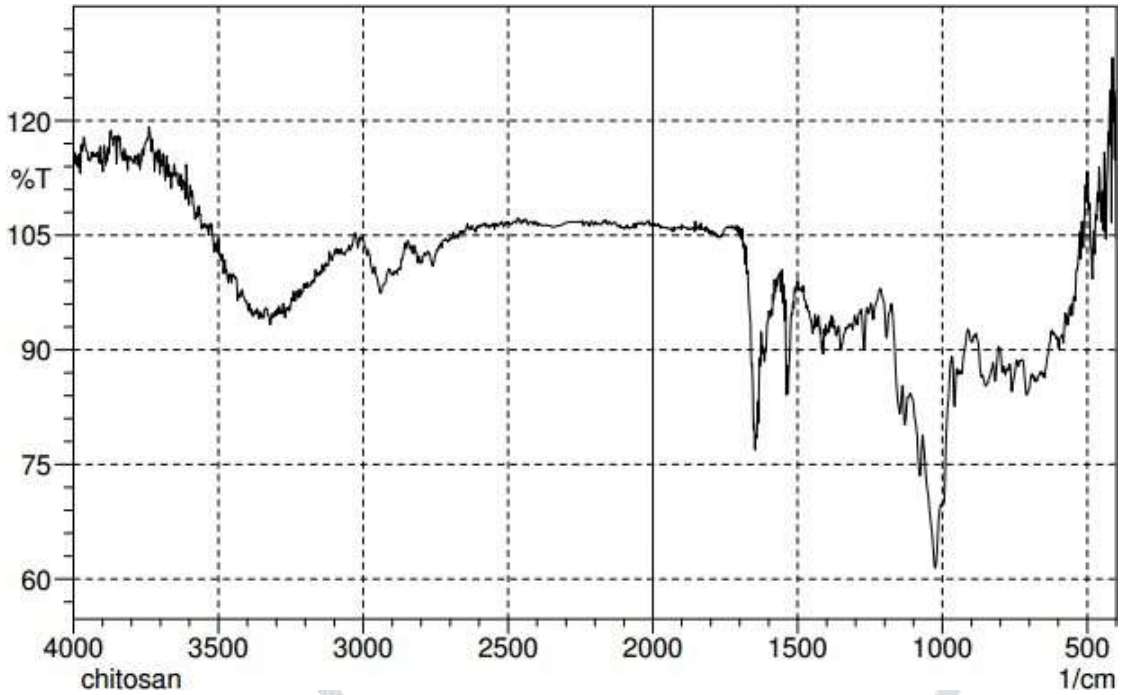


Figure 9: FTIR Spectra of chitosan

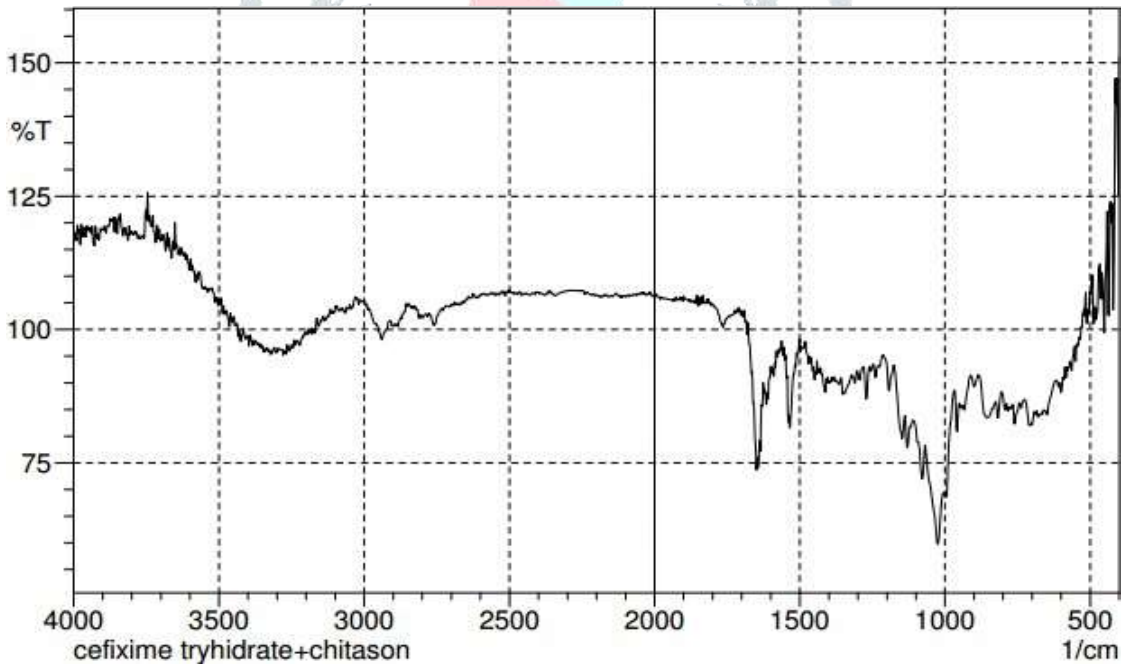


Figure 10: FTIR Spectra of CFT+ chitosan

Table no.7: FTIR-Spectral data of CFT and mixture of CFT-chitosan

Functional group	Frequency cm^{-1}		
	CFT	**Chitosan**	**CFT+ Chitosan**
C=C stretching	1589.34	1539.2	1533.41
C-N stretching	1170.79	1147.65	1192.01
C-Cl stretching	1093.64	1078.21	1024.02
C-=O	1664.4		1664.4

Discussion:-

In FTIR analysis, the spectrum showed of CFT an intense well – defined bands at C=O stretching at 1666.5 1/cm, C=C stretching 1589 1/cm, C- Cl stretching 1093.64 1/cm & C-N stretch at 1170.79 1/cm. The IR spectrum of chitosan C=C stretching 1533.41 1/cm, C- Cl stretching 1078.21 1/cm & C-N stretch at 1147.65 1/cm. & 8751/cm showed C-H out of plane bending of the ring. The combination of the drug with polymer showed C=C, C-N, C-Cl & C=O stretching in table no13. FTIR Spectroscopy was utilized to determine the similarity of CFT with excipients. Individual medication and medication with excipients were independently filtered. Both spectra were looked at for affirmation of normal groups. IR spectra are accounted for CFT and were discovered to be good with chitosan utilized.

6. Differential Scanning Calorimetriy:

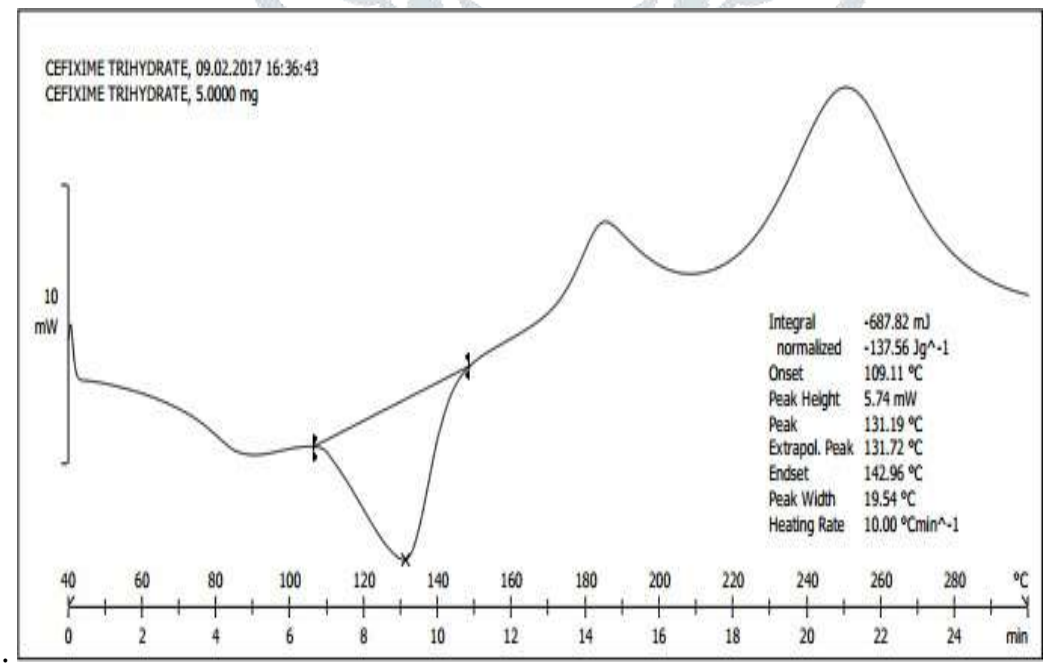


Figure 11: DSC spectra of CFT

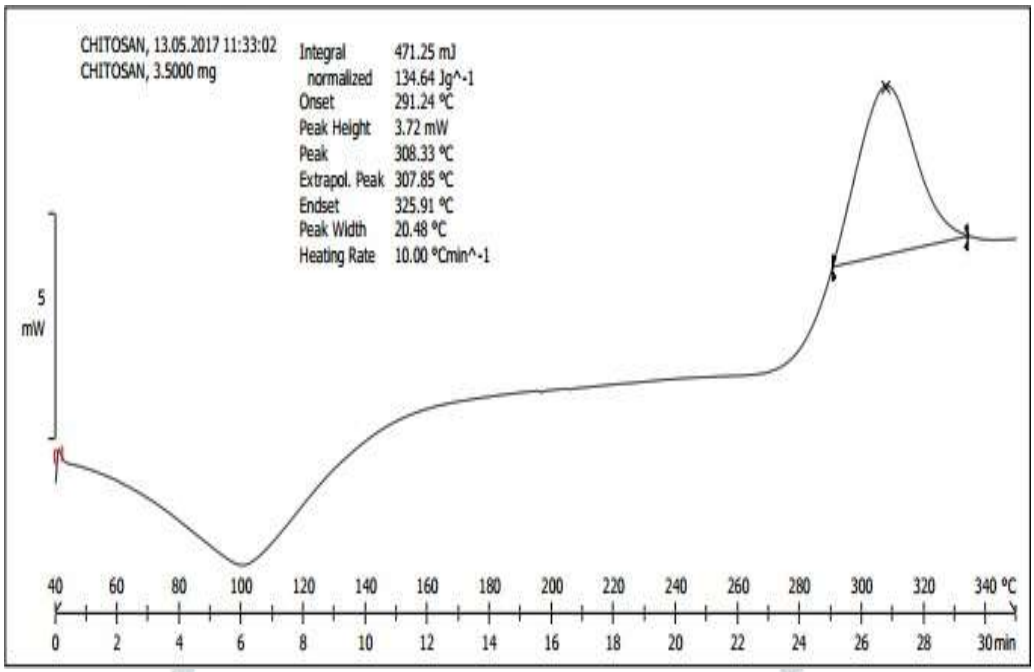


Figure 12: DSC spectra of chitosan

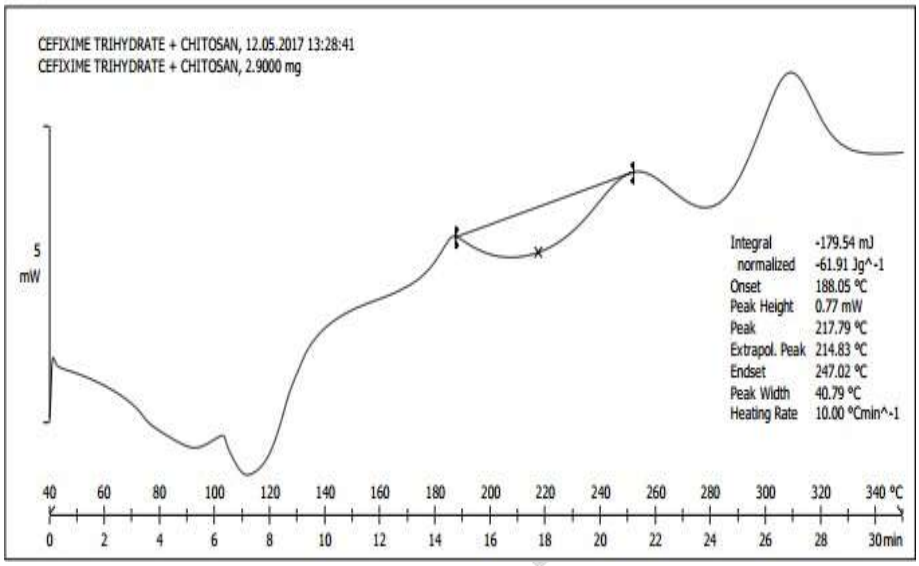


Figure 13: DSC spectra of CFT+ chitosan

Discussion:-

The thermal analysis of CFT was done to see the melting point of it was found to be 131.19°c. The thermogram of CFT is shown in Fig no.22. The melting point of chitosan was found to be 308.33°c. & thermal analysis of CFT with polymer was done to see the melting point of 217.79°c. Compatibility studies showed slight interaction between the drug and polymer, by thermal analysis studies.

7. Formulation Design

The CFT film has formulated and evaluated as per below table.10 different formulation has been prepared by varying concentrations of CFT like 10 %, 20%, 30% w/w of chitosan wt. The drug concentration has been varied based on the literature survey. The glutaraldehyde & distilled water used for the preparation of chitosan polymeric solution. The drug-loaded non CL periodontal film from F1 –F4 & CL from F5 – F10 by different exposure time in glutaraldehyde vapor for 2 & 4 hr.

8. Morphological properties of dental films:

All films were visually inspected for properties such as size and smoothness was found to be uniform in the prepared batches. But color variation occurs in crossed linked formulation **(F5 –F10)** shows pale yellow color because of the reaction of film formulation with glutaraldehyde vapors & uncrossed linked formulation shows dark brown.

Weight uniformity films: Drug loaded films (7×2 mm) were tested for uniformity of weight. The results of weight uniformity showed that the films found uniform in weight. The average weight of the films was found in the range of 3.44 mg to 6.9 mg. The maximum average weight was found for formulation F4 (6.9 mg) and a minimum for formulation F6 (3.44 mg). & % of weight variation of all formulation showed weight 8.118 mg -21.99mg. Maximum weight variation was found for formulation F10 (21.99mg) & minimum for formulation F1 (8.11mg). It is quite evident that the weight of the film is directly proportional to the amount of CFT in each formulation.

Thickness: The loaded film was tested for Drug loaded film was tested for thickness by using a vernier caliper. From the result, it was inferred that F5 (0.383) has the least thickness whereas the F1 (0.861mm) has the highest thickness.

Percentage moisture loss: From the result, it was inferred that F1 & F5 (50) has the highest moisture loss whereas F8 (14.28) has the lowest moisture loss

Table no.8: Physicochemical characterization of CFT loaded chitosan films.

Sr. no.	Film code	Average weight (mg)	% Weight uniformity (mg)	Thickness (mm)	% moisture Loss	% Content uniformity
1	F1	4.04	8.118	0.861	16.66	13.01
2	F2	4.38	14.79	0.569	50.00	87.65

3	F3	6.84	12.71	0.856	25.00	87.75
4	F4	6.9	14.48	0.82	20.00	96.20
5	F5	3.84	16.32	0.383	50.00	94.20
6	F6	3.44	19.06	0.407	33.33	99.45
7	F7	5.3	15.76	0.446	28.57	95.00
8	F8	4.5	17.71	0.517	14.28	91.12
9	F9	3.92	15.91	0.469	28.57	96.15
10	F10	3.9	21.99	0.545	16.66	99.10

Swelling index: All the prepared formulations (F1 to F10) of CFT dental films were evaluated for the swelling index. The swelling index was found maximum for formulation F3 & F9 (100 %) and minimum for formulation F4 (25%). Figure no.23 is a comparative chart showing the swelling index of different film formulations (from F1 to F10).

Table no.8: Swelling index data of **F1-F10** formulation

Sr. no	**Film code**	**% Swelling index**			
		15min	**30min**	**45min**	**60min**
1	F1	16.66	33.33	66.66	83.33
2	F2	33.33	55	55	66.66
3	F3	33.33	66.66	83.33	100
4	F4	8.3	8.3	16.66	25
5	F5	33.33	50	50	50
6	F6	33.33	50	50	66.66
7	F7	8.33	11.11	33.33	33.33
8	F8	8.33	11.11	33.33	44.44
9	F9	33.33	83	100	100
10	F10	11.11	22.22	33.33	44.44

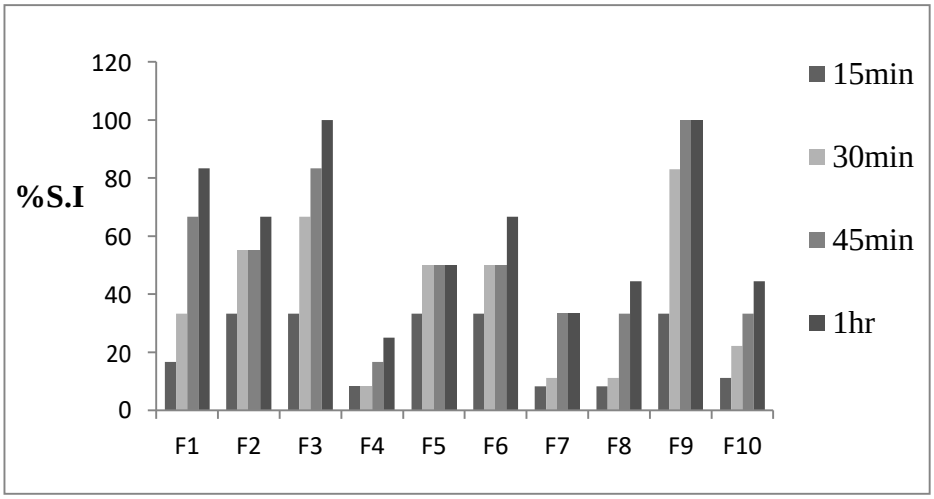


Figure 14: Comparative value of swelling index of **F1-F10**

9. *In vitro* % DR study:

***In-vitro* % DR study of Uncross-linked formulations Table**

no.9: % of DR of Un-CLfilms **(F1-F4)**

Time (days)	1	2	3	4	5	6	7
F1	2.05	3.37	4.47	5.08	8.90	12.34	13.02
F2	65.57	67.21	69.02	70.74	74.43	80.38	87.68
F3	42.77	51.58	56.35	63.84	66.87	73.27	87.79
F4	**72.68**	**76.79**	**78.58**	**83.00**	**86.40**	**91.14**	**96.23**

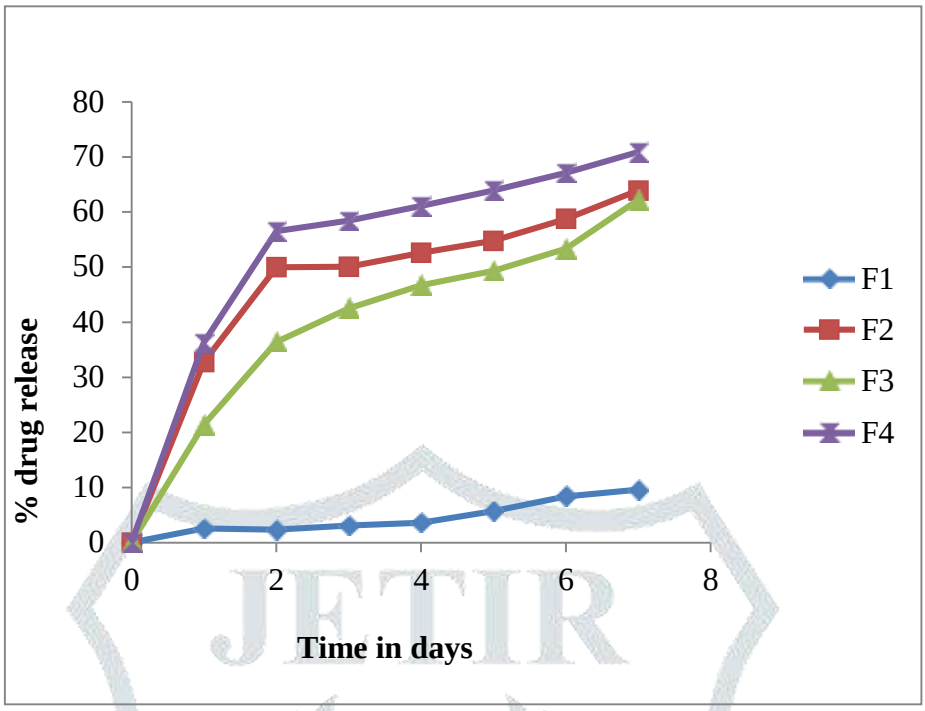


Figure 15: % DR of F1-F4

10. *In-vitro* % DR study of CL formulation

Table no.10: % of DR CL films **(F5-F10)**

Time in days	1	2	3	4	5	6	7	8	9	10	11	12
F5	55.85	71.45	77.67	82.04	84.89	85.76	89.64	89.87	90.95	92.35	92.45	94.23
F6	55.85	72.68	78.61	83.56	87.53	87.98	92.41	92.81	94.59	96.50	98.09	99.45
F7	61.96	66.70	72.02	76.33	81.06	84.63	87.14	90.69	91.89	93.35	93.66	95.01
F8	80.08	82.80	84.36	85.89	87.20	88.54	89.99	91.12	92.86	94.19	94.46	95.57
F9	66.20	70.35	72.75	73.70	76.60	77.66	78.35	80.15	80.25	94.00	95.05	96.15
F10	65.40	65.85	66.42	70.19	70.89	81.34	87.53	91.96	94.96	95.67	98.66	99.10

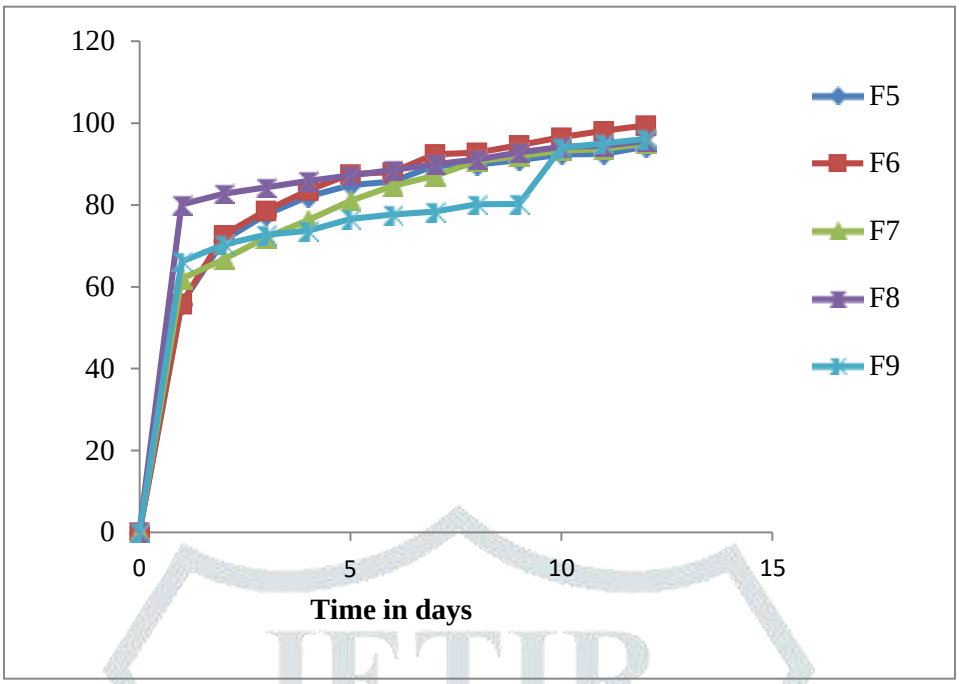


Figure 16: % DR of F5-F10

Discussion:-

The release time profile for different concentrations of CFT from Chitosan films is shown in Figure 26. The release profile showed that there was the rapid initial release of the drug on day one, that is, 65.57, 42.77, & 72.68 for 10, 20, and 30% of the drug-loaded films, respectively. A perusal of Figure 26 indicated that the initial rapid release must have been because of the burst effect, due to the elution of the drugs from the outer surface and cut edges of the matrix. Once the burst effect was completed, the slow and sustained release was seen up to seven days. At the end of seven days the amount of DR was found to be 87.68, 87.79, &
96.23 for 10, 20, and 30% of the drug-loaded films, respectively. In comparison, the cross- linked films also showed a burst effect initially followed by sustained release of the drug, but up to 12 days, with more uniformity of DR per day. The two-hour and four-hour cross-linked films showed 99.45, 95.57, 99.10, and 94.23, 95.01, 96.15 for 30, 20, 10% drug release, respectively, at the end of 12 days. The release time profile for crossed linked formulations shown in fig no.27

11. *In -vitro* DR kinetics

Table no.11: Kinetic values obtained from different plots of CFT-loaded films

Sr no.	Film code	%Cumulative DRplots R2	Zero-order plots R2	First-order plots R2	Higuchi plots R2
1	F1	0.8891	0.926	0.9979	0.7997
2	F2	0.8217	0.9056	1	0.8757
3	**F3**	**0.9276**	**0.9778**	**0.9998**	**0.9626**
4	F4	0.8018	0.9875	0.9999	0.8757
5	F5	0.6162	0.7717	0.995	0.7491
6	F6	0.764	**0.9627**	0.9993	0.8634
7	F7	0.8147	0.9421	0.9997	0.9108
8	F8	0.6024	0.9853	0.9997	0.7141
9	F9	0.8451	0.8981	1	0.949
10	F10	0.8841	0.9448	0.9998	0.8883

Discussion:-

The dissolution rate-controlled release was ruled out. Hence data was fit according to Higuchi's diffusion model as the plots showed linearity (R2: 0.7491 to 0.9626). Thus, the cumulative percentage of DR versus the square root of the time in days was calculated. The greater crosslinking time in CL formulation resulting in more sustained release of a drug, the % DR variation at 12 days for CL films because of variation in cross-linking time.

VII. SUMMARY & CONCLUSION

Several delivery systems have been examined for use in periodontal disease, but still, an ideal targeted delivery system is yet to be developed. The utmost advantages related to the use of intra-pocket delivery systems over systemic delivery are that the administration is less time consuming than mechanical debridement and a lesser amount of drug is enough to attain actual concentration at the site. Compatibility studies exhibited no interaction between the drug and polymer, by FTIR studies. The drug was incorporated into Chitosan and fabricated as a film in three altered concentrations 10, 20, and 30% w/w to the weight of the polymer. The films containing the drug

content (10, 20, & 30% w/w) were further cross-linked with glutaraldehyde 2%, which was aimed to extend and control the drug release for more number of days. The drug-loaded Chitosan films were flexible and influenced good tensile strength, and the physicochemical evaluation constraints were found to be satisfactory. As the films were cross-linked, the tensile strength of the films was reduced, but cross-linking had a definite influence on the release rate of the drug. The films were stable in all respects and did not show any signs of degradation when stored in the refrigerator or at room temperature. The in-vitro antibacterial activity studies explained the positive effect on periodontal pathogens. The in-vitro release studies showed an initial burst release of the drug by more than 40% and the release was sustained up to seven days and 12 days for the non-cross-linked and cross- linked films, respectively. Through the % release study, the films persisted intact, without any disintegration. The order of release of the drug was found to be zero order first order and followed the Higuchi model. From the above studies it can be concluded that the drug(s) were found to release at a constant rate, so Chitosan may be a useful matrix for sustained release of drugs, and crosslinking of the polymer is essential for the management of adult periodontitis. The advantage of Chitosan is that it has a wound healing property, which is a positive effect on anti-bacterial therapy. Since Chitosan is bioadhesive and biodegradable, it is immobile when left in-situ and degrades as the time advances.

- *In-vitro* Antibacterial activity work in progress.

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